IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	DAIICHI SANKYO COMPANY, LIMITED and UBE INDUSTRIES, LTD.
Patent No.	:	5,288,726
Patent Issue Date	:	February 22, 1994
Application Serial No.	:	07/941,676
Application Filing Date	:	September 8, 1992
Inventors	:	Hiroyuki KOIKE; Fumitoshi ASAI; Atsuhiro SUGIDACHI; Tomio KIMURA; Teruhiko INOUE; Shigeyoshi NISHINO; Yasunori TSUZAKI
For	:	TETRAHYDROTHIENOPYRIDINE DERIVATIVES, FURO AND PYRROLO ANALOGS THEREOF AND THEIR PREPARATION AND USES FOR INHIBITING BLOOD PLATELET AGGREGATION
Attorneys for Applicants	:	Frishauf, Holtz, Goodman & Chick, P.C. 220 Fifth Avenue, 16th Floor New York, New York 10001-7708 E-Mail Address: BARTH@FHGC-LAW.COM
Customer No.	:	01933
Attorney Docket No.	:	920676EXT/HG

TRANSMITTAL OF AN APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

MAIL STOP HATCH WAXMAN PTE

Attention: Ms. Mary Till

S I R:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (including an original and two copies) of the above-

captioned patent for a product approved on July 10, 2009.

The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-delivered to the U.S. Patent and Trademark Office.

Enclosed is a Form PTO-2038 for the prescribed fee in the amount of $1,120.00 for the application presented.

In the event the actual fee differs from the Form PTO-2038 enclosed herewith, it is requested that the overpayment or underpayment be credited or charged to Deposit Account No. 06-1378.

Respectfully submitted,

Date: August 11, 2009

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Encs.: (1) An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 and attachments thereto

(2) Two additional copies of APPLICATION FOR EXTENSION OF PATENT TERM and attachments thereto

(3) Form PTO-2038 in the amount of $1,120.00

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 USC 156 FOR U.S. PATENT NO. 5,288,726

Applicants	:	DAIICHI SANKYO COMPANY, LIMITED and UBE INDUSTRIES LTD.
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APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

MAIL STOP HATCH WAXMAN PTE

S I R :

Pursuant to 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, and in accordance with the

provisions of 35 USC 156, Daiichi Sankyo Company, Limited, a corporation of Japan, having a place of business at 3-5-1 Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426, Japan and Ube Industries, Ltd., a corporation of Japan, having a place of business at 1978-96, Oaza Kogushi, Ube-shi, Yamaguchi 755-8633, Japan (hereinafter referred to collectively as "Applicants"), the assignees of record of United States Patent No. 5,288,726, hereby apply for an extension of 1,679 days of the term of United States Patent No. 5,288,726, issued February 22, 1994 on patent application Serial No. 07/941,676, filed September 8, 1992.

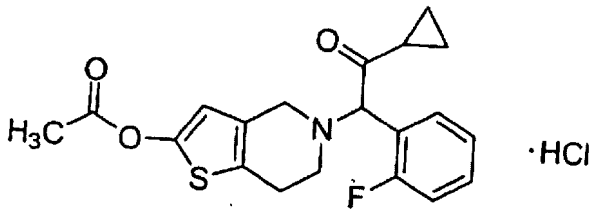
The following information is submitted in accordance with 35 USC 156(d) and 37 CFR 1.740, and follows the numerical format set forth in 37 CFR 1.740.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure and characteristics;

The approved product is Effient™.

The chemical name of the active ingredient of Effient™ is 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, of which the generic name is prasugrel hydrochloride. Prasugrel hydrochloride is further characterized as follows:

The chemical formula of prasugrel hydrochloride is as follows:



- Molecular formula: $C_{20}H_{20}FNO_3S \cdot HCl$

- Molecular weight: 409.90

A letter of the marketing applicant, Eli Lilly and Company ("Eli Lilly") (attached hereto as Exhibit 1) provides authorization to the Applicants to rely on the activities and data of the marketing applicant before the Food and Drug Administration in obtaining approval of Effient™.

A copy of the PACKAGE INSERT for Effient™ is attached hereto as Exhibit 2.

(2) A complete identification of the Federal Statute including the applicable provision of law under which the regulatory review occurred;

Effient™ was subject to regulatory review under Section 505 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") (21 USC 355).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

Effient™ was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to §505(b) of the FD&C Act on July 10, 2009 (see Exhibit 3 (APPROVAL LETTER)).

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved;

The active ingredient in Effient™ is 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (prasugrel hydrochloride). The active ingredient in Effient™ has not been previously approved for commercial marketing or use under the FD&C Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty (60) day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted;

The product was approved for commercial marketing on July 10, 2009, and the last day within the sixty (60) day period permitted for submission of an application for extension (pursuant to 37 CFR 1.720(f)) of the patent is September 7, 2009. The date of submission of the present application is no later than September 7, 2009 and, therefore, the present application for extension of patent term has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

The patent for which an extension is being sought is identified as follows:

U.S. Patent No. : 5,288,726

Issue Date : February 22, 1994

Inventors	:	Hiroyuki KOIKE; Fumitoshi ASAI; Atsuhiro SUGIDACHI; Tomio KIMURA; Teruhiko INOUE; Shigeyoshi NISHINO; Yasunori TSUZAKI
For	:	TETRAHYDROTHIENOPYRIDINE DERIVATIVES, FURO AND PYRROLO ANALOGS THEREOF AND THEIR PREPARATION AND USES FOR INHIBITING BLOOD PLATELET AGGREGATION
Application Serial No.	:	07/941,676
Application Filing Date	:	September 8, 1992
Expiration Date (unless extended)	:	September 8, 2012

The application that issued as United States Patent No. 5,288,726 was assigned from the inventors to the Applicants by an Assignment recorded on September 9, 1992 in the United States Patent and Trademark Office at Reel 6252, Frame 0610. A Merger document was recorded on June 13, 2007 in the United States Patent and Trademark Office at Reel 019419, Frame 0711, wherein the name of one of the assignees, namely Sankyo Company, Limited, was changed to Daiichi Sankyo Company, Limited.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims and drawings);

A copy of United States Patent No. 5,288,726, for which an extension is being sought, is attached as Exhibit 4 (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;

No disclaimer or reexamination certificate has been issued for United States Patent No. 5,288,726.

A copy of the Certificate of Correction for United States Patent No. 5,288,726 dated April 21, 1998 is attached herewith as Exhibit 5.

Copies of each of three receipts for maintenance fee payments for United States Patent No. 5,288,726, received from the United States Patent and Trademark Office, are attached hereto as Exhibits 6A, 6B and 6C.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product;

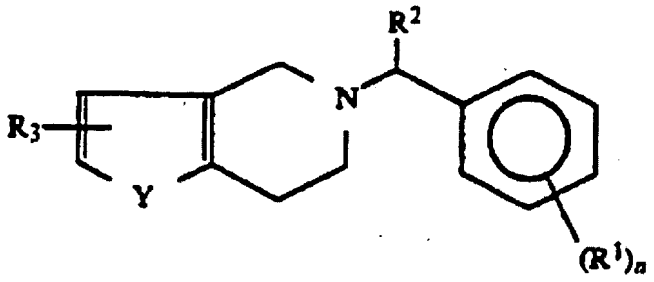
(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

United States Patent No. 5,288,726 claims the approved product, Effient™. Claims 1, 3 to 24, 28, 42 to 47, 54 and 56 claim the approved product. Claims 48 to 53 claim a method for the treatment or prophylaxis of thrombosis or embolisms by administering the approved product.

The manner in which each applicable patent claim reads on the approved product is as follows:

Claim 1 of United States Patent No. 5,288,726 ("USP 5,288,726") recites a compound of formula (I):



(I)

wherein

R^1 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halogen atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 1 to 10 carbon atoms; a substituted alkanoyl group which has from 2 to 10 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below; an alkenoyl group having from 3 to 6 carbon

atoms; a substituted alkenoyl group which has from 3 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below; a cycloalkylcarbonyl group having from 4 to 8 carbon atoms; a substituted cycloalkylcarbonyl group which has from 4 to 8 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below; or a substituted benzoyl group having at least one substituent selected from the group consisting of substituents B, defined below;

R^3 represents a hydrogen atom; a hydroxy group; an alkoxy group having from 1 to 4 carbon atoms; a substituted alkoxy group which has from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents C, defined below; an aralkyloxy group in which the aralkyl part is as defined below; an alkanoyloxy group having from 1 to 18 carbon atoms; an alkenoyloxy group having from 3 to 6 carbon atoms; a cycloalkylcarbonyloxy group having from 4 to 8 carbon atoms; an arylcarbonyloxy group in which the aryl part is as defined below; an alkoxycarbonyloxy group having from 2 to 5 carbon atoms; an aralkyloxycarbonyloxy group in which the aralkyl part is as defined below; a phthalidyloxy group; a (5-methyl-2-oxo-1,3-dioxolen-4yl)methoxy group; a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group; a group of formula $-NR^aR^b$: wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, alkyl groups having from 1 to 4 carbon atoms and substituted alkyl groups which have from 1 to 4 carbon atoms and which are

substituted by at least one substituent selected from the group consisting of substituents C, defined below; an aralkylamino group in which the aralkyl part is as defined below; an alkanoylamino group having from 1 to 18 carbon atoms; an alkenoylamino group having from 3 to 6 carbon atoms; a cycloalkylcarbonylamino group having from 4 to 8 carbon atoms: an arylcarbonylamino group in which the aryl part is as defined below; an alkoxycarbonylamino group having from 2 to 5 carbon atoms; an aralkyloxycarbonylamino group in which the aralkyl part is as defined below; a phthalidylamino group; a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylamino group; a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methylamino group, or a nitro group;

Y is a sulfur atom; and

n is an integer from 1 to 5, and, when n is an integer from 2 to 5, the groups represented by R^1 may be the same as or different from each other;

said substituents A are selected from the group consisting of halogen atoms, hydroxy groups, alkoxy groups having from 1 to 4 carbon atoms and cyano groups;

said substituents B are selected from the group consisting of alkyl groups having from 1 to 4 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms;

said substituents C are selected from the group consisting of alkoxy groups having from 1 to 4 carbon atoms, alkanoyloxy groups having from 1 to 6 carbon atoms and arylcarbonyloxy groups in which the aryl part is as defined below;

said aralkyl parts of said aralkyloxy, aralkyloxycarbonyloxy, aralkylamino and aralkyloxycarbonylamino groups are alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one aryl groups as defined below;

said aryl groups and said aryl parts of said arylcarbonyloxy groups and of said arylcarbonylamino groups having from 6 to 10 carbon atoms in a carbocyclic ring which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D, defined below; and

said substituents D are selected from the group consisting of the groups and atoms defined above in relation to R^1, other than said hydrogen atom;

or a tautomer thereof, or a pharmaceutically acceptable salt of said compound of formula (I) and of said tautomer.

When in claim 1, R^1 is a halogen atom, R^2 is a cycloalkylcarbonyl group having from 4 to 8 carbon atoms, R^3 is an alkanoyloxy group having from 1 to 18 carbon atoms, Y is a sulfur atom, n is an integer from 1 to 5, and there is a pharmaceutically acceptable salt of the compound of the formula (I), claim 1 includes prasugrel hydrochloride, i.e., 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride. Therefore, claim 1 reads on the approved product.

Claim 3 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^2, R^3, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^1 is restricted. In the restricted definition, R^1 can be a halogen atom. Therefore, claim 3 reads on the approved product.

Claim 4 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^3, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^2 is restricted. In the restricted definition, R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms. Therefore, claim 4 reads on the approved product.

Claim 5 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^3 is restricted. In the restricted definition, R^3 can be an alkanoyloxy group having from 1 to 18 carbon atoms. Therefore, claim 5 reads on the approved product.

Claim 6 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 1 to 18 carbon atoms. Therefore, claim 6 reads on the approved product.

Claim 7 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, R^3, Y, and the pharmaceutically acceptable salt are the same as in

claim 6, but the definition of n is restricted. In the restricted definition, n can be an integer from 1 to 3. Therefore, claim 7 reads on the approved product.

Claim 8 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, R^3, Y, and the pharmaceutically acceptable salt are the same as in claim 6, but the definition of n is restricted. In the restricted definition, n can be an integer 1. Therefore, claim 8 reads on the approved product.

Claim 9 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^2, R^3, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^1 is restricted. In the restricted definition R^1 can be a halogen atom. Therefore, claim 9 reads on the approved product.

Claim 10 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^3, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^2 is restricted. In the restricted definition, R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms. Therefore, claim 10 reads on the approved product.

Claim 11 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^3 is restricted. In the restricted definition, R^3 can be an alkanoyloxy group having from 1 to 12 carbon atoms. Therefore, claim 11 reads on the approved product.

Claim 12 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 1 to 12 carbon atoms. Therefore, claim 12 reads on the approved product.

Claim 13 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, R^3, Y, and the pharmaceutically acceptable salt are the same as in claim 12, but the definition of n is restricted. In the restricted definition, n can be an integer from 1 to 3. Therefore, claim 13 reads on the approved product.

Claim 14 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, R^3, Y, and the pharmaceutically acceptable salt are the same as in claim 12, but the definition of n is restricted. In the restricted definition, n can be an integer 1. Therefore, claim 14 reads on the approved product.

Claim 15 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^2, R^3, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^1 is restricted. In the restricted definition, R^1 can be a halogen atom. Therefore, claim 15 reads on the approved product.

Claim 16 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^3 is restricted. In the restricted definition, R^3 can be an alkanoyloxy group having from 2 to 10 carbon atoms. Therefore, claim 16 reads on the approved product.

Claim 17 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 2 to 10 carbon atoms. Therefore, claim 17 reads on the approved product.

Claim 18 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, R^3, Y, and the pharmaceutically acceptable salt are the same as in

claim 17, but the definition of n is restricted. In the restricted definition, n can be an integer from 1 to 3. Therefore, claim 18 reads on the approved product.

Claim 19 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, R^3, Y, and the pharmaceutically acceptable salt are the same as in claim 17, but the definition of n is restricted. In the restricted definition, n can be an integer 1. Therefore, claim 19 reads on the approved product.

Claim 20 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^3, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^2 is restricted. In the restricted definition, R^2 can be a cyclopropylcarbonyl group. Therefore, claim 20 reads on the approved product.

Claim 21 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^3 is restricted. In the restricted definition, R^3 can be an alkanoyloxy group having from 2 to 6 carbon atoms. Therefore, claim 21 reads on the approved product.

Claim 22 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but

the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a fluorine atom; R^2 can be a cyclopropylcarbonyl group; and R^3 can be an alkanoyloxy group having from 2 to 6 carbon atoms. Therefore, claim 22 reads on the approved product.

Claim 23 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, R^3, Y, and the pharmaceutically acceptable salt are the same as in claim 22, but the definition of n is restricted. In the restricted definition, n can be an integer from 1 to 3. Therefore, claim 23 reads on the approved product.

Claim 24 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^1, R^2, R^3, Y, and the pharmaceutically acceptable salt are the same as in claim 22, but the definition of n is restricted. In the restricted definition, n can be an integer 1. Therefore, claim 24 reads on the approved product.

Claim 28 of USP 5,288,726 recites the compounds of the formula (I) of claim 1 and a pharmaceutically acceptable salt thereof, in which the compound is 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine. Therefore, claim 28 reads on the approved product.

Claim 42 of USP 5,288,726 recites a pharmaceutical composition comprising an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof, as claimed in claim 1. Therefore, claim 42 embraces a pharmaceutical composition containing the approved product and thus reads on the approved product.

Claim 43 of USP 5,288,726 recites a pharmaceutical composition of claim 42 which comprises an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor is at least one compound of formula (I) of claim 1, in which the definitions of Y, n, the pharmaceutically acceptable salt, the pharmaceutically acceptable carrier, and the diluent are the same as in claim 42, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 1 to 18 carbon atoms. Therefore, claim 43 embraces a pharmaceutical composition containing the approved product and thus reads on the approved product.

Claim 44 of USP 5,288,726 recites a pharmaceutical composition of claim 42 which comprises an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said

inhibitor is at least one compound of formula (I) of claim 1, in which the definitions of Y, n, the pharmaceutically acceptable salt, the pharmaceutically acceptable carrier, and the diluent are the same as in claim 42, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 1 to 12 carbon atoms. Therefore, claim 44 embraces a pharmaceutical composition containing the approved product and thus reads on the approved product.

Claim 45 of USP 5,288,726 recites a pharmaceutical composition of claim 42 which comprises an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor is at least one compound of formula (I) of claim 1, in which the definitions of Y, n, the pharmaceutically acceptable salt, the pharmaceutically acceptable carrier, and the diluent are the same as in claim 42, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 2 to 10 carbon atoms. Therefore, claim 45 embraces a pharmaceutical composition containing the approved product and thus reads on the approved product.

Claim 46 of USP 5,288,726 recites a pharmaceutical composition of claim 42 which comprises an effective amount of a

blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor is at least one compound of formula (I) of claim 1, in which the definitions of Y, n, the pharmaceutically acceptable salt, the pharmaceutically acceptable carrier, and the diluent are the same as in claim 42, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a fluorine atom; R^2 can be a cyclopropylcarbonyl group; and R^3 can be an alkanoyloxy group having from 2 to 6 carbon atoms. Therefore, claim 46 embraces a pharmaceutical composition containing the approved product and thus reads on the approved product.

Claim 47 of USP 5,288,726 recites a pharmaceutical composition which comprises an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor includes 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof. Therefore, claim 47 embraces a pharmaceutical composition containing the approved product and thus reads on the approved product.

Claim 48 of USP 5,288,726 recites a method for the treatment or prophylaxis of thrombosis or embolisms which comprises administering to a mammal an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof, as claimed in claim 1.

Therefore, claim 48 reads on an approved use of the approved product.

Claim 49 of USP 5,288,726 recites a method for the treatment or prophylaxis of thrombosis or embolisms of claim 48 which comprises administering to a mammal an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I) of claim 1, in which the definitions of Y, n, and the pharmaceutically acceptable salt are the same as in claim 1, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 1 to 18 carbon atoms. Therefore, claim 49 reads on an approved use of the approved product.

Claim 50 of USP 5,288,726 recites a method for the treatment or prophylaxis of thrombosis or embolisms of claim 48 which comprises administering to a mammal an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I) of claim 1, in which the definitions of Y, n, and the pharmaceutically acceptable salt are the same as in claim 1, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 1 to 12 carbon atoms. Therefore, claim 50 reads on an approved use of the approved product.

Claim 51 of USP 5,288,726 recites a method for the treatment or prophylaxis of thrombosis or embolisms of claim 48 which comprises administering to a mammal an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I) of claim 1, in which the definitions of Y, n, and the pharmaceutically acceptable salt are the same as in claim 1, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a halogen atom; R^2 can be a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; and R^3 can be an alkanoyloxy group having from 2 to 10 carbon atoms. Therefore, claim 51 reads on an approved use of the approved product.

Claim 52 of USP 5,288,726 recites a method for the treatment or prophylaxis of thrombosis or embolisms of claim 48 which comprises administering to a mammal an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I) of claim 1, in which the definitions of Y, n and the pharmaceutically acceptable salt are the same as in claim 1, but the definitions of R^1, R^2 and R^3 are restricted. In the restricted definitions, R^1 can be a fluorine atom; R^2 can be a cyclopropylcarbonyl group; and R^3 can be an alkanoyloxy group having from 2 to 6 carbon atoms. Therefore, claim 52 reads on an approved use of the approved product.

Claim 53 of USP 5,288,726 recites a method for the treatment or prophylaxis of thrombosis or embolisms of claim 48 which comprises administering to a mammal an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor

includes 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and the pharmaceutically acceptable salts thereof. Therefore, claim 53 reads on an approved use of the approved product.

Claim 54 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of R^2, R^3, Y, n, and the pharmaceutically acceptable salt are the same as in claim 1, but the definition of R^1 is restricted. In the restricted definition, R^1 can be a fluorine atom. Therefore, claim 54 reads on the approved product.

Claim 56 of USP 5,288,726 recites the compounds of the formula (I) of claim 1, in which the definitions of n and the pharmaceutically acceptable salt are the same as in claim 1, but the definitions of R^1, R^2, R^3 and Y are restricted. In the restricted definitions, R^1 can be a fluorine atom; R^2 can be a cyclopropylcarbonyl group; and R^3 can be an alkanoyloxy group having from 2 to 6 carbon atoms. In the restricted definition, Y is a sulfur atom. Therefore, claim 56 reads on the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 USC 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

The relevant dates and information pursuant to 35 USC 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

The IND was assigned number 63,449 by the FDA.

The IND became effective on November 16, 2001, which is thirty (30) days after receipt of the investigational new drug (IND) application by the FDA.

This establishes the beginning of the "regulatory review period" under 35 USC 156(g)(1) as of November 16, 2001.

On December 26, 2007, a new drug application (NDA 22-307) was submitted by Eli Lilly under §505(b) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") and §314.50 of Title 21 of the Code of Federal Regulations for the Effient™ (prasugrel hydrochloride).

NDA 22-307 for Effient™ (prasugrel hydrochloride) was approved on July 10, 2009. Attached as Exhibit 3 (APPROVAL LETTER) is a copy of a letter dated July 10, 2009 from the FDA approving NDA 22-307 for Effient™ (prasugrel hydrochloride).

Thus, for the purposes of determining the "regulatory review period" under 35 USC §156(g)(1), July 10, 2009 is

the date of the first approval of Effient™ (prasugrel hydrochloride).

Summary of the Most Relevant Dates

October 16, 2001	:	IND for Effient™ (prasugrel hydrochloride) submitted
October 17, 2001	:	Receipt by the FDA of the IND for Effient™ (prasugrel hydrochloride)
November 16, 2001	:	IND 63,449 for Effient™ (prasugrel hydrochloride) became effective
December 26, 2007	:	NDA 22-307 for Effient™ (prasugrel hydrochloride) was submitted
July 10, 2009	:	NDA 22-307 for Effient™ (prasugrel hydrochloride) was approved

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

An IND for Effient™ (prasugrel hydrochloride) was submitted on October 16, 2001, which became effective on November 16, 2001. The studies under the IND are summarized in the attached Exhibit 7 (IND LOG). These studies were used to support NDA 22-307, which was submitted on December 26, 2007.

Subsequent to the submission of the aforesaid NDA, personnel of Eli Lilly had numerous contacts and meetings with FDA personnel with respect to the new drug application, and these are summarized in the attached Exhibit 8 (NDA LOG).

(12) A statement beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined;

The requirements under 35 USC 156(a) and 35 USC 156(c)(4) have been satisfied as follows:

Statement of Eligibility of the Patent for Extension
Under §35 USC 156(a) and (c)(4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 USC §156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the

provision of law under which such regulatory review period occurred; and §156(c)(4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding letters, each of these elements is satisfied herein as follows:

(a) The statutory term of U.S. Patent No. 5,288,726 expires on September 8, 2012. This Application for Extension of Patent Term has, therefore, been submitted before the expiration of the patent term.

(b) The term of U.S. Patent No. 5,288,726 has never been extended.

(c) This Application for Extension of Patent Term is submitted by the owners of record, namely Daiichi Sankyo Company, Limited and Ube Industries, Ltd. This Application for Extension of Patent Term is submitted in accordance with 35 USC §156(d) in that it is submitted within the sixty (60) day

period beginning on the date, July 10, 2009, that the product received permission for marketing under the Federal Food, Drug, and Cosmetic Act and contains the information required under 35 USC §156(d).

(d) As evidenced by the July 10, 2009 letter from the FDA, Exhibit 3 (APPROVAL LETTER), the product was subject to a regulatory review period under §505(b)(1) of the FD&C Act before its commercial marketing or use.

(e) The permission for the commercial marketing of Effient™ (prasugrel hydrochloride) after regulatory review under §505(b)(1) is the first permitted commercial marketing of Effient™ (prasugrel hydrochloride). This is confirmed by the absence of any approved new drug application under which Effient™ (prasugrel hydrochloride) could be commercially marketed prior to July 10, 2009.

Statement as to Length of Extension Claimed
in Accordance with 37 USC §1.775

The length of extension of the term of U.S. Patent No. 5,288,726 of 1,679 days to extend to April 14, 2017 as claimed by the applicants was determined according to the provisions of 37 CFR 1.775(c) and (d) is as follows:

According to 37 CFR 1.775(b), the term of the patent is extended by the length of the regulatory review period for the product, reduced as appropriate according to paragraph (d)(1) through (d)(6) of 37 CFR 1.775.

The period of extension is determined in accordance with 35 USC §156 and follows the format set forth in 37 CFR 1.775(c) and (d).

37 CFR §1.775(c). The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 USC §156(g)(1)(B), it is the sum of:

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act;

The number of days between the effective date of the IND, November 16, 2001, and the initial submission of NDA 22-307, December 26, 2007, is a period of 2,232 days, and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of NDA 22-307 on December 26, 2007, to approval of NDA 22-307 on July 10, 2009 is a period of 563 days.

37 CFR §1.775(d). The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by -

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period;

(i) The number of days in the period of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on November 16, 2001, which were on or before February 22, 1994, the date the patent issued, is a period of 0 days;

2,232 days minus 0 days equals 2,232 days, and

the number of days in the period of the NDA initial submission of NDA 22-307 on December 26, 2007, and approval on July 10, 2009 which were on or before February 22, 1994, the date the patent issued, is a period of 0 days.

563 days minus 0 days equals 563 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 USC 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the Applicants did not act with due diligence is 0 days, therefore

2,232 days minus 0 days equals 2,232 days;

563 days minus 0 days equals 563 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2,232 days equals 1,116 days.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent, as shortened by any terminal disclaimer;

1,116 days + 563 days = 1,679 days.

Adding 1,679 days to September 8, 2012, the original term of the patent (no terminal disclaimer was made), extends the term to April 14, 2017.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to July 10, 2009, the date of approval of the Application, results in the date of July 10, 2023.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is April 14, 2017.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

Adding 5 years to the original expiration date of the patent (September 8, 2012) results in the date of September 8, 2017.

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

Comparing April 14, 2017 and September 8, 2017, the earlier date is April 14, 2017 and therefore the patent term should be extended to April 14, 2017.

(6) If the original patent was issued before September 24, 1984, and ....

This is not applicable for United States Patent No. 5,288,726.

(13) A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see §1.765);

Applicants acknowledge a duty to disclose to the Director of the United States Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of the 1,679 days extension being sought to the term of United States Patent No. 5,288,726.

(14) The prescribed fee for receiving and acting upon the application for extension (see §1.20(j));

Form PTO-2038 in the amount of One Thousand One Hundred Twenty Dollars ($1,120) in payment of the prescribed fee for receiving and acting upon the application for extension is enclosed herewith.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Please address inquiries and correspondence relating to the application for patent term extension to:

Richard S. Barth, Esq.
Frishauf, Holtz, Goodman
& Chick, P.C.
220 Fifth Avenue, 16th Fl.
New York, NY 10001-7708
Tel. No. (212) 319-4900
Fax No.: (212) 319-5101
E-Mail: BARTH@FHGC-LAW.COM.

(16) The application under this section must be accompanied by two additional copies of such application (for a total of three copies) (37 C.F.R. 1.740(b);

In addition to the present application for extension of the patent term of U.S. Patent No. 5,288,726, also submitted herewith are two additional complete copies, for a total of three copies of the present application.

(17) Signature Requirements in accordance with 37 C.F.R. 1.730;

The present application for extension of the term of U.S. Patent No. 5,288,726 is submitted on behalf of the patent owners by a registered practitioner who is authorized to act on behalf of the patent owners.

Frishauf, Holtz, Goodman
& Chick, P.C.
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New York, NY 10001-7708
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(212) 319-4551/Ext. 219
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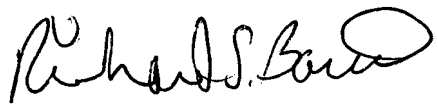
RSB/ddf

Respectfully submitted,



Richard S. Barth
Reg. No. 28,180

EXHIBIT 1
LETTER OF MARKETING APPLICANT

www.lilly.com

Eli Lilly and Company
P.O. Box 6288
Indianapolis, Indiana 46206-6288
USA

Phone: 317- 276-2000

July14, 2009

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

MAIL STOP: HATCH WAXMAN PTE

RE: Application for Extension of Patent Term Under 35 USC 156 for U.S. Patent No. 5,288,726

Sir:

I, Douglas K. Norman, am Vice President and General Patent Counsel of Eli Lilly and Company (hereinafter referred to as "Eli Lilly") state as follows:

1. Eli Lilly and Company has a place of business at Lilly Corporate Center, Drop 1104, Indianapolis, Indiana 46285.

2. Eli Lilly and Company filed IND 63,449 and NDA 22-307 with the U.S. Food and Drug Administration for commercial marketing approval of Effient™ (prasugrel hydrochloride) pursuant to §505(b) of the Federal Food Drug and Cosmetic Act.

3. During the entire regulatory review period there was an agency relationship between Eli Lilly and Company, the marketing applicant, Daiichi Sankyo Company, Limited (including its predecessor, Sankyo Company, Limited) and Ube Industries, Limited, the owners of U.S. Patent No. 5,288,726.

4. Eli Lilly hereby authorizes Daiichi Sankyo Company, Limited and Ube Industries, Limited to rely on the activities of Eli Lilly and Company in connection with IND 63,449 and NDA 22-307 in support of Daiichi Sankyo and Ube Industries' application under 35 U.S.C. sec. 156 for extension of U.S. Patent No. 5,288,726.

Very truly yours,

Douglas K. Norman

Douglas K. Norman
Vice President and
General Patent Counsel

EXHIBIT 2
PACKAGE INSERT FOR EFFIENT™

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Effient safely and effectively. See full prescribing information for Effient.

EFFIENT (prasugrel) tablets
Initial U.S. Approval: 2009

WARNING: BLEEDING RISK

See full prescribing information for complete boxed warning

Effient can cause significant, sometimes fatal, bleeding (5.1, 5.2, and 6.1).

Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke (4.1 and 4.2).

In patients ≥ 75 years of age, Effient is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered (8.5).

Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery.

Additional risk factors for bleeding include:

- **body weight < 60 kg**
- **propensity to bleed**
- **concomitant use of medications that increase the risk of bleeding**

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient.

If possible, manage bleeding without discontinuing Effient. Stopping Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events (5.3).

----------INDICATIONS AND USAGE----------

Effient is a $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows:

- Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI) (1.1)
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI (1.1).

----------DOSAGE AND ADMINISTRATION----------

- Initiate treatment with a single 60 mg oral loading dose (2).
- Continue at 10 mg once daily with or without food. Consider 5 mg once daily for patients < 60 kg (2).
- Patients should also take aspirin (75 mg to 325 mg) daily (2).

----------DOSAGE FORMS AND STRENGTHS----------

5 mg and 10 mg tablets (3)

----------CONTRAINDICATIONS----------

- Active pathological bleeding (4.1)
- Prior transient ischemic attack or stroke (4.2)

----------WARNINGS AND PRECAUTIONS----------

- CABG-related bleeding: Risk increases in patients receiving Effient who undergo CABG (5.2).
- Discontinuation of Effient: Premature discontinuation increases risk of stent thrombosis, MI, and death (5.3).

----------ADVERSE REACTIONS----------

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BLEEDING RISK

Effient can cause significant, sometimes fatal, bleeding *[see Warnings and Precautions (5.1 and 5.2) and Adverse Reactions (6.1)]*.

Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke *[see Contraindications (4.1 and 4.2)]*.

In patients ≥ 75 years of age, Effient is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered *[see Use in Specific Populations (8.5)]*.

Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery.

Additional risk factors for bleeding include:

- **body weight < 60 kg**
- **propensity to bleed**
- **concomitant use of medications that increase the risk of bleeding (*e.g.*, warfarin, heparin, fibrinolytic therapy, chronic use of non-steroidal anti-inflammatory drugs [NSAIDS])**

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient.

If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome

Effient™ is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death *[see Clinical Studies (14)]*.

It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial *[see Warnings and Precautions (5.2)]*. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.

2 DOSAGE AND ADMINISTRATION

Initiate Effient treatment as a single 60 mg oral loading dose and then continue at 10 mg orally once daily. Patients taking Effient should also take aspirin (75 mg to 325 mg) daily *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*. Effient may be administered with or without food *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

Dosing in Low Weight Patients

Compared to patients weighing ≥ 60 kg, patients weighing < 60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg once daily maintenance dose. Consider lowering the maintenance dose to 5 mg in patients < 60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied.

3 DOSAGE FORMS AND STRENGTHS

Effient 5 mg is a yellow, elongated hexagonal, film-coated, non-scored tablet debossed with "5 MG" on one side and "4760" on the other side.

Effient 10 mg is a beige, elongated hexagonal, film-coated, non-scored tablet debossed with "10 MG" on one side and with "4759" on the other side.

4 CONTRAINDICATIONS

4.1 Active Bleeding

Effient is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

4.2 Prior Transient Ischemic Attack or Stroke

Effient is contraindicated in patients with a history of prior transient ischemic attack (TIA) or stroke. In TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel), patients with a history of TIA or ischemic stroke (> 3 months prior to enrollment) had a higher rate of stroke on Effient (6.5%; of which 4.2% were thrombotic stroke and 2.3% were intracranial hemorrhage [ICH]) than on clopidogrel (1.2%; all thrombotic). In patients without such a history, the incidence of stroke was 0.9% (0.2% ICH) and 1.0% (0.3% ICH) with Effient and clopidogrel, respectively. Patients with a history of ischemic stroke within 3 months of screening and patients with a history of hemorrhagic stroke at any time were excluded from TRITON-TIMI 38. Patients who experience a stroke or TIA while on Effient generally should have therapy discontinued *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Thienopyridines, including Effient, increase the risk of bleeding. With the dosing regimens used in TRITON-TIMI 38, TIMI (Thrombolysis in Myocardial Infarction) Major (clinically overt bleeding associated with a fall in hemoglobin ≥ 5 g/dL, or intracranial hemorrhage) and TIMI Minor (overt bleeding associated with a fall in hemoglobin of ≥ 3 g/dL but < 5 g/dL) bleeding events were more common on Effient than on clopidogrel *[see Adverse Reactions (6.1)]*. The bleeding risk is highest initially, as shown in Figure 1 (events through 450 days; inset shows events through 7 days).

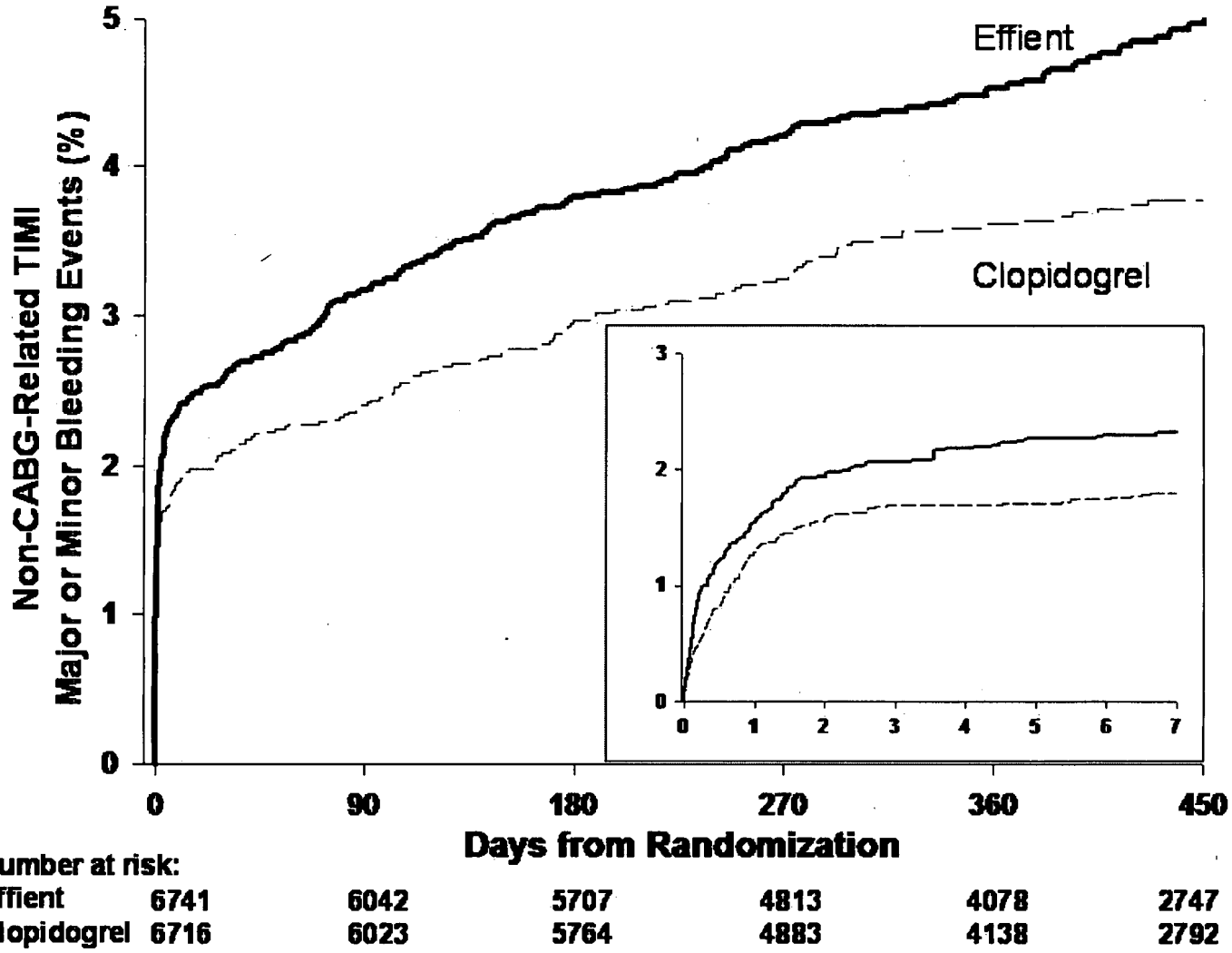


Figure 1: Non-CABG-Related TIMI Major or Minor Bleeding Events

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures even if the patient does not have overt signs of bleeding.

Do not use Effient in patients with active bleeding, prior TIA or stroke *[see Contraindications (4.1 and 4.2)]*.

Other risk factors for bleeding are:

- Age ≥ 75 years. Because of the risk of bleeding (including fatal bleeding) and uncertain effectiveness in patients ≥ 75 years of age, use of Effient is generally not recommended in these patients, except in high-risk situations (patients with diabetes or history of myocardial infarction) where its effect appears to be greater and its use may be considered *[see Adverse Reactions (6.1), Use in Specific Populations (8.5), Clinical Pharmacology (12.3), and Clinical Trials (14)]*.
- CABG or other surgical procedure *[see Warnings and Precautions (5.2)]*.
- Body weight < 60 kg. Consider a lower (5 mg) maintenance dose *[see Dosage and Administration (2), Adverse Reactions (6.1), Use in Specific Populations (8.6)]*.
- Propensity to bleed (*e.g.*, recent trauma, recent surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, or severe hepatic impairment) *[see Adverse Reactions (6.1) and Use in Specific Populations (8.8)]*.
- Medications that increase the risk of bleeding (*e.g.*, oral anticoagulants, chronic use of non-steroidal anti-inflammatory drugs [NSAIDs], and fibrinolytic agents). Aspirin and heparin were commonly used in TRITON-TIMI 38 *[see Drug Interactions (7), Clinical Studies (14)]*.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of prasugrel's active metabolite is short relative to the lifetime of the platelet, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.

5.2 Coronary Artery Bypass Graft Surgery-Related Bleeding

The risk of bleeding is increased in patients receiving Effient who undergo CABG. If possible, Effient should be discontinued at least 7 days prior to CABG.

Of the 437 patients who underwent CABG during TRITON-TIMI 38, the rates of CABG-related TIMI Major or Minor bleeding were 14.1% in the Effient group and 4.5% in the clopidogrel group *[see Adverse Reactions (6.1)]*. The higher risk for bleeding events in patients treated with Effient persisted up to 7 days from the most recent dose of study drug. For patients receiving a thienopyridine within 3 days prior to CABG, the frequencies of TIMI Major or Minor bleeding were 26.7% (12 of 45 patients) in the Effient group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.4% (3 of 89 patients) in the clopidogrel group.

Do not start Effient in patients likely to undergo urgent CABG. CABG-related bleeding may be treated with transfusion of blood products, including packed red blood cells and platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.

5.3 Discontinuation of Effient

Discontinue thienopyridines, including Effient, for active bleeding, elective surgery, stroke, or TIA. The optimal duration of thienopyridine therapy is unknown. In patients who are managed with PCI and stent placement, premature discontinuation of any antiplatelet medication, including thienopyridines, conveys an increased risk of stent thrombosis, myocardial infarction, and death. Patients who require premature discontinuation of a thienopyridine will be at increased risk for cardiac events. Lapses in therapy should be avoided, and if thienopyridines must be temporarily discontinued because of an adverse event(s), they should be restarted as soon as possible *[see Contraindications (4.1 and 4.2) and Warnings and Precautions (5.1)]*.

5.4 Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) has been reported with the use of other thienopyridines, sometimes after a brief exposure (< 2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment, including plasmapheresis (plasma exchange). TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragment red blood cells] seen on peripheral smear), neurological findings, renal dysfunction, and fever.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following serious adverse reactions are also discussed elsewhere in the labeling:

- Bleeding *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]*
- Thrombotic thrombocytopenic purpura *[see Warnings and Precautions (5.4)]*

Safety in patients with ACS undergoing PCI was evaluated in a clopidogrel-controlled study, TRITON-TIMI 38, in which 6741 patients were treated with Effient (60 mg loading dose and 10 mg once daily) for a median of 14.5 months (5802 patients were treated for over 6 months; 4136 patients were treated for more than 1 year). The population treated with Effient was 27 to 96 years of age, 25% female, and 92% Caucasian. All patients in the TRITON-TIMI 38 study were to receive aspirin. The dose of clopidogrel in this study was a 300 mg loading dose and 75 mg once daily.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials cannot be directly compared with the rates observed in other clinical trials of another drug and may not reflect the rates observed in practice.

Drug Discontinuation

The rate of study drug discontinuation because of adverse reactions was 7.2% for Effient and 6.3% for clopidogrel. Bleeding was the most common adverse reaction leading to study drug discontinuation for both drugs (2.5% for Effient and 1.4% for clopidogrel).

Bleeding

Bleeding Unrelated to CABG Surgery - In TRITON-TIMI 38, overall rates of TIMI Major or Minor bleeding adverse reactions unrelated to coronary artery bypass graft surgery (CABG) were significantly higher on Effient than on clopidogrel, as shown in Table 1.

Table 1: Non-CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)	p-value
TIMI Major or Minor bleeding	4.5	3.4	p=0.002
TIMI Major bleeding[b]	2.2	1.7	p=0.029
Life-threatening	1.3	0.8	p=0.015
Fatal	0.3	0.1	
Symptomatic intracranial hemorrhage (ICH)	0.3	0.3	
Requiring inotropes	0.3	0.1	
Requiring surgical intervention	0.3	0.3	
Requiring transfusion (≥4 units)	0.7	0.5	
TIMI Minor bleeding[b]	2.4	1.9	p=0.022

[a] Patients may be counted in more than one row.

[b] See 5.1 for definition.

Figure 1 demonstrates non-CABG related TIMI Major or Minor bleeding. The bleeding rate is highest initially, as shown in Figure 1 (inset: Days 0 to 7) *[see Warnings and Precautions (5.1)]*.

Bleeding rates in patients with the risk factors of age ≥ 75 years and weight < 60 kg are shown in Table 2.

Table 2: Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)

	Major/Minor		Fatal	
	Effient (%)	Clopidogrel (%)	Effient (%)	Clopidogrel (%)
Weight < 60kg (N=308 Effient, N=356 clopidogrel)	10.1	6.5	0.0	0.3
Weight ≥ 60kg (N=6373 Effient, N=6299 clopidogrel)	4.2	3.3	0.3	0.1
Age < 75 years (N=5850 Effient, N=5822 clopidogrel)	3.8	2.9	0.2	0.1
Age ≥ 75 years (N=891 Effient, N=894 clopidogrel)	9.0	6.9	1.0	0.1

Bleeding Related to CABG - In TRITON-TIMI 38, 437 patients who received a thienopyridine underwent CABG during the course of the study. The rate of CABG-related TIMI Major or Minor bleeding was 14.1% for the Effient group and 4.5% in the clopidogrel group (Table 3). The higher risk for bleeding adverse reactions in patients treated with Effient persisted up to 7 days from the most recent dose of study drug.

Table 3: CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) (N=213)	Clopidogrel (%) (N=224)
TIMI Major or Minor bleeding	14.1	4.5
TIMI Major bleeding	11.3	3.6
Fatal	0.9	0
Reoperation	3.8	0.5
Transfusion of ≥5 units	6.6	2.2
Intracranial hemorrhage	0	0
TIMI Minor bleeding	2.8	0.9

[a] Patients may be counted in more than one row.

Bleeding Reported as Adverse Reactions - Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 were, for Effient and clopidogrel, respectively: epistaxis (6.2%, 3.3%), gastrointestinal hemorrhage (1.5%, 1.0%), hemoptysis (0.6%, 0.5%), subcutaneous hematoma (0.5%, 0.2%), post-procedural hemorrhage (0.5%, 0.2%), retroperitoneal hemorrhage (0.3%, 0.2%), and retinal hemorrhage (0.0%, 0.1%).

Malignancies

During TRITON-TIMI 38, newly diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. It is unclear if these observations are causally-related or are random occurrences.

Other Adverse Events

In TRITON-TIMI 38, common and other important non-hemorrhagic adverse events were, for Effient and clopidogrel, respectively: severe thrombocytopenia (0.06%, 0.04%), anemia (2.2%, 2.0%), abnormal hepatic function (0.22%, 0.27%), allergic reactions (0.36%, 0.36%), and angioedema (0.06%, 0.04%). Table 4 summarizes the adverse events reported by at least 2.5% of patients.

Table 4: Non-Hemorrhagic Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group

	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)
Hypertension	7.5	7.1
Hypercholesterolemia/Hyperlipidemia	7.0	7.4
Headache	5.5	5.3
Back pain	5.0	4.5
Dyspnea	4.9	4.5
Nausea	4.6	4.3
Dizziness	4.1	4.6
Cough	3.9	4.1
Hypotension	3.9	3.8
Fatigue	3.7	4.8
Non-cardiac chest pain	3.1	3.5
Atrial fibrillation	2.9	3.1
Bradycardia	2.9	2.4
Leukopenia (< 4 x 10^9 WBC/L)	2.8	3.5
Rash	2.8	2.4
Pyrexia	2.7	2.2
Peripheral edema	2.7	3.0
Pain in extremity	2.6	2.6
Diarrhea	2.3	2.6

7 DRUG INTERACTIONS

7.1 Warfarin

Coadministration of Effient and warfarin increases the risk of bleeding *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

7.2 Non-Steroidal Anti-Inflammatory Drugs

Coadministration of Effient and NSAIDs (used chronically) may increase the risk of bleeding *[see Warnings and Precautions (5.1)]*.

7.3 Other Concomitant Medications

Effient can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes *[see Clinical Pharmacology (12.3)]*.

Effient can be administered with aspirin (75 mg to 325 mg per day), heparin, GPIIb/IIIa inhibitors, statins, digoxin, and drugs that elevate gastric pH, including proton pump inhibitors and H_2 blockers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B - There are no adequate and well-controlled studies of Effient use in pregnant women. Reproductive and developmental toxicology studies in rats and rabbits at doses of up to 30 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite) revealed no evidence of fetal harm; however, animal studies are not always predictive of a human response. Effient should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In embryo fetal developmental toxicology studies, pregnant rats and rabbits received prasugrel at maternally toxic oral doses equivalent to more than 40 times the human exposure. A slight decrease in pup body weight was observed; but, there were no structural malformations in either species. In prenatal and postnatal rat studies, maternal treatment with prasugrel had no effect on the behavioral or reproductive development of the offspring at doses greater than 150 times the human exposure *[see Nonclinical Toxicology (13.1)]*.

8.3 Nursing Mothers

It is not known whether Effient is excreted in human milk; however, metabolites of Effient were found in rat milk. Because many drugs are excreted in human milk, prasugrel should be used during nursing only if the potential benefit to the mother justifies the potential risk to the nursing infant.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

In TRITON-TIMI 38, 38.5% of patients were ≥65 years of age and 13.2% were ≥75 years of age. The risk of bleeding increased with advancing age in both treatment groups, although the relative risk of bleeding (Effient compared with clopidogrel) was similar across age groups.

Patients ≥ 75 years of age who received Effient had an increased risk of fatal bleeding events (1.0%) compared to patients who received clopidogrel (0.1%). In patients ≥ 75 years of age, symptomatic intracranial hemorrhage occurred in 7 patients (0.8%) who received Effient and in 3 patients (0.3%) who received clopidogrel. Because of the risk of bleeding, and because effectiveness is uncertain in patients ≥ 75 years of age *[see Clinical Studies (14)]*, use of Effient is generally not recommended in these patients, except in high-risk situations (diabetes and past history of myocardial infarction) where its effect appears to be greater and its use may be considered *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.6 Low Body Weight

In TRITON-TIMI 38, 4.6% of patients treated with Effient had body weight <60 kg. Individuals with body weight < 60 kg had an increased risk of bleeding and an increased exposure to the active metabolite of prasugrel *[see Dosage and Administration (2), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*. Consider lowering the maintenance dose to 5 mg in patients <60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied.

8.7 Renal Impairment

No dosage adjustment is necessary for patients with renal impairment. There is limited experience in patients with end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B). The pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease have not been studied, but such patients are generally at higher risk of bleeding *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.9 Metabolic Status

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.

10 OVERDOSAGE

10.1 Signs and Symptoms

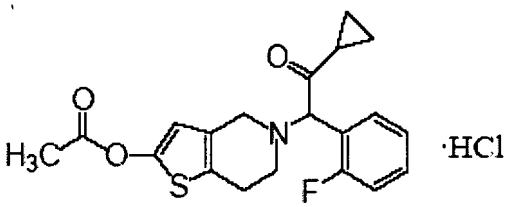
Platelet inhibition by prasugrel is rapid and irreversible, lasting for the life of the platelet, and is unlikely to be increased in the event of an overdose. In rats, lethality was observed after administration of 2000 mg/kg. Symptoms of acute toxicity in dogs included emesis, increased serum alkaline phosphatase, and hepatocellular atrophy. Symptoms of acute toxicity in rats included mydriasis, irregular respiration, decreased locomotor activity, ptosis, staggering gait, and lacrimation.

10.2 Recommendations about Specific Treatment

Platelet transfusion may restore clotting ability. The prasugrel active metabolite is not likely to be removed by dialysis.

11 DESCRIPTION

Effient contains prasugrel, a thienopyridine class inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor. Effient is formulated as the hydrochloride salt, a racemate, which is chemically designated as 5-[(1RS)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride. Prasugrel hydrochloride has the empirical formula $C_{20}H_{20}FNO_3S \cdot HCl$ representing a molecular weight of 409.90. The chemical structure of prasugrel hydrochloride is:



Prasugrel hydrochloride is a white to practically white solid. It is soluble at pH 2, slightly soluble at pH 3 to 4, and practically insoluble at pH 6 to 7.5. It also dissolves freely in methanol and is slightly soluble in 1- and 2-propanol and acetone. It is practically insoluble in diethyl ether and ethyl acetate.

Effient is available for oral administration as 5 mg or 10 mg elongated hexagonal, film-coated, non-scored tablets, debossed on each side. Each yellow 5 mg tablet is manufactured with 5.49 mg prasugrel hydrochloride, equivalent to 5 mg prasugrel and each beige 10 mg tablet with 10.98 mg prasugrel hydrochloride, equivalent to 10 mg of prasugrel. During manufacture and storage, partial conversion from prasugrel hydrochloride to prasugrel free base may occur. Other ingredients include mannitol, hypromellose,

croscarmellose sodium, microcrystalline cellulose, and vegetable magnesium stearate. The color coatings contain lactose, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (only in Effient 10 mg tablet).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.

12.2 Pharmacodynamics

Prasugrel produces inhibition of platelet aggregation to 20 μM or 5 μM ADP, as measured by light transmission aggregometry. Following a 60-mg loading dose of Effient, approximately 90% of patients had at least 50% inhibition of platelet aggregation by 1 hour. Maximum platelet inhibition was about 80% (Figure 2). Mean steady-state inhibition of platelet aggregation was about 70% following 3 to 5 days of dosing at 10 mg daily after a 60-mg loading dose of Effient.

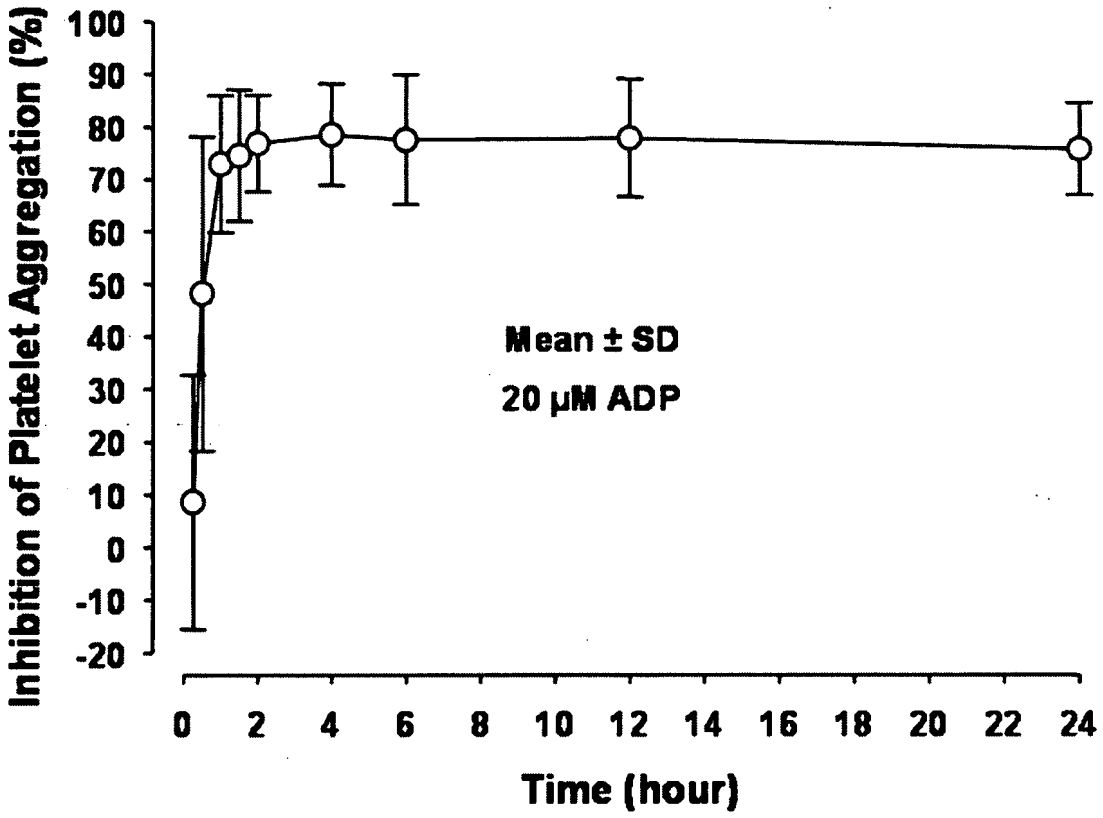


Figure 2: Inhibition (Mean±SD) of 20 μM ADP-induced Platelet Aggregation (IPA) Measured by Light Transmission Aggregometry after Prasugrel 60 mg

Platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation of prasugrel, this time course being a reflection of new platelet production rather than pharmacokinetics of prasugrel. Discontinuing clopidogrel 75 mg and initiating prasugrel 10 mg with the next dose resulted in increased inhibition of platelet aggregation, but not greater than that typically produced by a 10 mg maintenance dose of prasugrel alone. The relationship between inhibition of platelet aggregation and clinical activity has not been established.

12.3 Pharmacokinetics

Prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. The active metabolite has an elimination half-life of about 7 hours (range 2-15 hours). Healthy subjects, patients with stable atherosclerosis, and patients undergoing PCI show similar pharmacokinetics.

Absorption and Binding - Following oral administration, ≥ 79% of the dose is absorbed. The absorption and metabolism are rapid, with peak plasma concentrations (C_{max}) of the active metabolite occurring approximately 30 minutes after dosing. The active metabolite's exposure (AUC) increases slightly more than proportionally over the dose range of 5 to 60 mg. Repeated daily doses of 10 mg do not lead to accumulation of the active metabolite. In a study of healthy subjects given a single 15 mg dose, the AUC of the

active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and T_{max} was increased from 0.5 to 1.5 hours. Effient can be administered without regard to food. The active metabolite is bound about 98% to human serum albumin.

Metabolism and Elimination - Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolyzed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The estimates of apparent volume of distribution of prasugrel's active metabolite ranged from 44 to 68 L and the estimates of apparent clearance ranged from 112 to 166 L/hr in healthy subjects and patients with stable atherosclerosis. The active metabolite is metabolized to two inactive compounds by S-methylation or conjugation with cysteine. The major inactive metabolites are highly bound to human plasma proteins. Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the feces as inactive metabolites.

Specific Populations

Pediatric - Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a pediatric population *[see Use in Specific Populations (8.4)]*.

Geriatric - In a study of 32 healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. In TRITON-TIMI 38, the mean exposure (AUC) of the active metabolite was 19% higher in patients ≥75 years of age than in patients <75 years of age *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Use in Specific Populations (8.5)]*.

Body Weight - The mean exposure (AUC) to the active metabolite is approximately 30 to 40% higher in subjects with a body weight of <60 kg than in those weighing ≥60 kg *[see Dosage and Administration (2), Warnings and Precautions (5.1), Adverse Reactions (6.1), and Use in Specific Populations (8.6)]*.

Gender - Pharmacokinetics of prasugrel's active metabolite are similar in men and women.

Ethnicity - Exposure in subjects of African and Hispanic descent is similar to that in Caucasians. In clinical pharmacology studies, after adjusting for body weight, the AUC of the active metabolite was approximately 19% higher in Chinese, Japanese, and Korean subjects than in Caucasian subjects.

Smoking - Pharmacokinetics of prasugrel's active metabolite are similar in smokers and nonsmokers.

Renal Impairment - Pharmacokinetics of prasugrel's active metabolite and its inhibition of platelet aggregation are similar in patients with moderate renal impairment (CrCL=30 to 50 mL/min) and healthy subjects. In patients with end stage renal disease, exposure to the active metabolite (both C_{max} and AUC(0-t_{last})) was about half that in healthy controls and patients with moderate renal impairment *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment - Pharmacokinetics of prasugrel's active metabolite and inhibition of platelet aggregation were similar in patients with mild to moderate hepatic impairment compared to healthy subjects. The pharmacokinetics and pharmacodynamics of prasugrel's active metabolite in patients with severe hepatic disease have not been studied *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.8)]*.

Drug Interactions

Potential for Other Drugs to Affect Prasugrel

Inhibitors of CYP3A - Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect prasugrel-mediated inhibition of platelet aggregation or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34% to 46%. Therefore, CYP3A inhibitors such as verapamil, diltiazem, indinavir, ciprofloxacin, clarithromycin, and grapefruit juice are not expected to have a significant effect on the pharmacokinetics of the active metabolite of prasugrel *[see Drug Interactions (7.3)]*.

Inducers of Cytochromes P450 - Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6 and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly change the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. Therefore, known CYP3A inducers such as rifampicin, carbamazepine, and other inducers of cytochromes P450 are not expected to have significant effect on the pharmacokinetics of the active metabolite of prasugrel *[see Drug Interactions (7.3)]*.

Drugs that Elevate Gastric pH - Daily coadministration of ranitidine (an H_2 blocker) or lansoprazole (a proton pump inhibitor) decreased the C_{max} of the prasugrel active metabolite by 14% and 29%, respectively, but did not change the active metabolite's AUC and T_{max}. In TRITON-TIMI 38, Effient was administered without regard to coadministration of a proton pump inhibitor or H_2 blocker *[see Drug Interactions (7.3)]*.

Statins - Atorvastatin (80 mg daily), a drug metabolized by CYP450 3A4, did not alter the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation *[see Drug Interactions (7.3)]*.

Heparin - A single intravenous dose of unfractionated heparin (100 U/kg) did not significantly alter coagulation or the prasugrel-mediated inhibition of platelet aggregation; however, bleeding time was increased compared with either drug alone *[see Drug Interactions (7.3)]*.

Aspirin - Aspirin 150 mg daily did not alter prasugrel-mediated inhibition of platelet aggregation; however, bleeding time was increased compared with either drug alone *[see Drug Interactions (7.3)]*.

Warfarin - A significant prolongation of the bleeding time was observed when prasugrel was coadministered with 15 mg of warfarin *[see Drug Interactions (7.1)]*.

Potential for Prasugrel to Affect Other Drugs

In vitro metabolism studies demonstrate that prasugrel's main circulating metabolites are not likely to cause clinically significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A, or induction of CYP1A2 or CYP3A.

Drugs Metabolized by CYP2B6 — Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel decreased exposure to hydroxybupropion, a CYP2B6-mediated metabolite of bupropion, by 23%, an amount not considered clinically

significant. Prasugrel is not anticipated to have significant effect on the pharmacokinetics of drugs that are primarily metabolized by CYP2B6, such as halothane, cyclophosphamide, propofol, and nevirapine.

Effect on Digoxin - The potential role of prasugrel as a Pgp substrate was not evaluated. Prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by prasugrel coadministration *[see Drug Interactions (7.3)]*.

12.5 Pharmacogenomics

There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - No compound-related tumors were observed in a 2-year rat study with prasugrel at oral doses up to 100 mg/kg/day (>100 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite). There was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses (>250 times the human metabolite exposure).

Mutagenesis - Prasugrel was not genotoxic in two *in vitro* tests (Ames bacterial gene mutation test, clastogenicity assay in Chinese hamster fibroblasts) and in one *in vivo* test (micronucleus test by intraperitoneal route in mice).

Impairment of Fertility - Prasugrel had no effect on fertility of male and female rats at oral doses up to 300 mg/kg/day (80 times the human major metabolite exposure at daily dose of 10 mg prasugrel).

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of Effient is derived from the TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel) study, a 13,608-patient, multicenter, international, randomized, double-blind, parallel-group study comparing Effient to a regimen of clopidogrel, each added to aspirin and other standard therapy, in patients with ACS (UA, NSTEMI, or STEMI) who were to be managed with PCI. Randomization was stratified for UA/NSTEMI and STEMI.

Patients with UA/NSTEMI presenting within 72 hours of symptom onset were to be randomized after undergoing coronary angiography. Patients with STEMI presenting within 12 hours of symptom onset could be randomized prior to coronary angiography. Patients with STEMI presenting between 12 hours and 14 days of symptom onset were to be randomized after undergoing coronary angiography. Patients underwent PCI, and for both UA/NSTEMI and STEMI patients, the loading dose was to be administered anytime between randomization and 1 hour after the patient left the catheterization lab. If patients with STEMI were treated with thrombolytic therapy, randomization could not occur until at least 24 hours (for tenecteplase, reteplase or alteplase) or 48 hours (for streptokinase) after the thrombolytic was given.

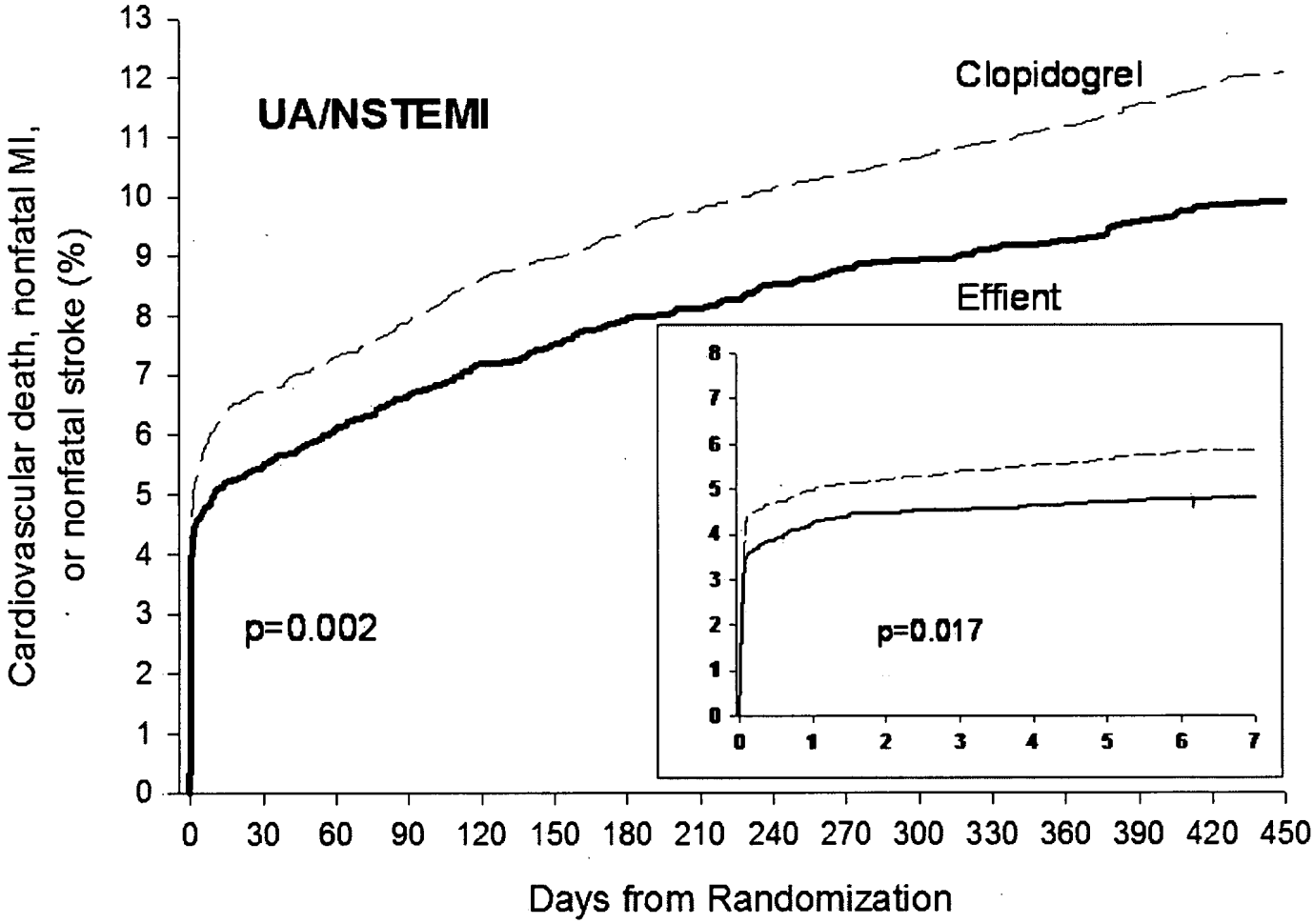
Patients were randomized to receive Effient (60 mg loading dose followed by 10 mg once daily) or clopidogrel (300 mg loading dose followed by 75 mg once daily), with administration and follow-up for a minimum of 6 months (actual median 14.5 months). Patients also received aspirin (75 mg to 325 mg once daily). Other therapies, such as heparin and intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, were administered at the discretion of the treating physician. Oral anticoagulants, other platelet inhibitors, and chronic NSAIDs were not allowed.

The primary outcome measure was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke in the UA/NSTEMI population. Success in this group allowed analysis of the same endpoint in the overall ACS and STEMI populations. Nonfatal MIs included both MIs detected solely through analysis of creatine kinase muscle-brain (CK-MB) changes and clinically apparent (investigator-reported) MIs.

The patient population was 92% Caucasian, 26% female, and 39% ≥65 years of age. The median time from symptom onset to study drug administration was 7 hours for patients with STEMI and 30 hours for patients with UA/NSTEMI. Approximately 99% of patients underwent PCI. The study drug was administered after the first coronary guidewire was placed in approximately 75% of patients.

Effient significantly reduced total endpoint events compared to clopidogrel (*see* Table 5 and Figure 3). The reduction of total endpoint events was driven primarily by a decrease in nonfatal MIs, both those occurring early (through 3 days) and later (after 3 days). Approximately 40% of MIs occurred peri-procedurally and were detected solely by changes in CK-MB. Administration of the clopidogrel loading dose in TRITON-TIMI 38 was delayed relative to the placebo-controlled trials that supported its approval for ACS. Effient produced higher rates of clinically significant bleeding than clopidogrel in TRITON-TIMI 38 *[see Adverse Reactions (6.1)]*. Choice of therapy requires balancing these differences in outcome.

The treatment effect of Effient was apparent within the first few days, and persisted to the end of the study (Figure 3). The inset shows results over the first 7 days.


UA/NSTEMI
Clopidogrel
Effient
p=0.002
p=0.017
Cardiovascular death, nonfatal MI, or nonfatal stroke (%)
Days from Randomization
0 30 60 90 120 150 180 210 240 270 300 330 360 390 420 450
0 1 2 3 4 5 6 7 8 9 10 11 12 13

398
399

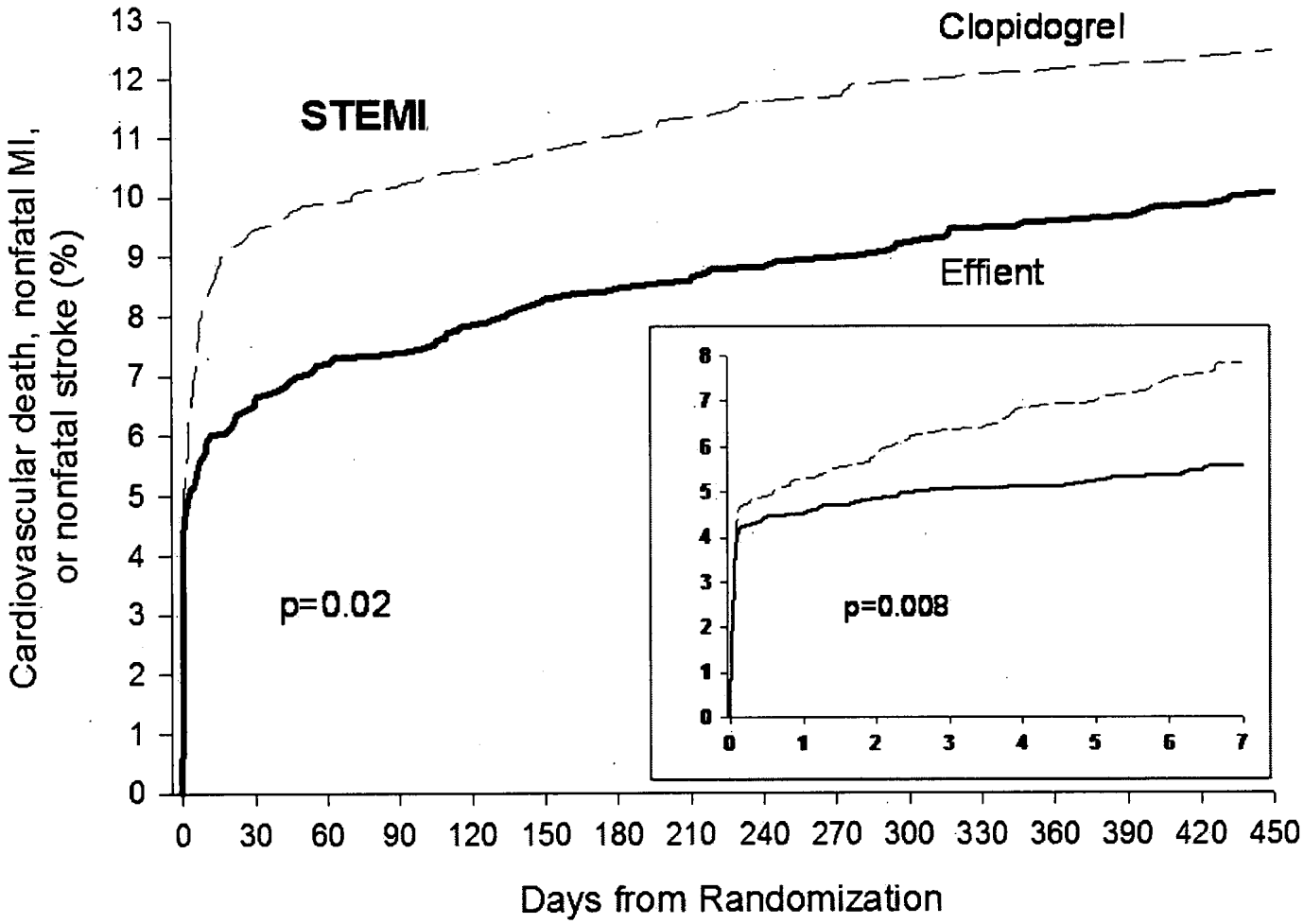


Figure 3: Time to first event of CV death, MI, or stroke (TRITON-TIMI 38)

The Kaplan-Meier curves (Figure 3) show the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke over time in the UA/NSTEMI and STEMI populations. In both populations, the curves separate within the first few hours. In the UA/NSTEMI population, the curves continue to diverge throughout the 15 month follow-up period. In the STEMI population, the early separation was maintained throughout the 15 month follow-up period, but there was no progressive divergence after the first few weeks.

Effient reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI populations (*see* Table 5). In patients who survived an on-study myocardial infarction, the incidence of subsequent events was also lower in the Effient group.

Table 5: Patients with Outcome Events (CV Death, MI, Stroke) in TRITON-TIMI 38

	Patients with events		From Kaplan-Meier analysis	
	Effient (%)	Clopidogrel (%)	Relative Risk Reduction (%)[a] (95% CI)	p-value
UA/NSTEMI	**N=5044**	**N=5030**		
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	18.0 (7.3, 27.4)	0.002
CV death	1.8	1.8	2.1 (-30.9, 26.8)	0.885
Nonfatal MI	7.1	9.2	23.9 (12.7, 33.7)	<0.001
Nonfatal Stroke	0.8	0.8	2.1 (-51.3, 36.7)	0.922
STEMI	**N=1769**	**N=1765**		
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	20.7 (3.2, 35.1)	0.019
CV death	2.4	3.3	26.2 (-9.4, 50.3)	0.129
Nonfatal MI	6.7	8.8	25.4 (5.2, 41.2)	0.016
Nonfatal Stroke	1.2	1.1	-9.7 (-104.0, 41.0)	0.77

[a] RRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase.

The effect of Effient in various subgroups is shown in Figures 4 and 5. Results are generally consistent across pre-specified subgroups, with the exception of patients with a history of TIA or stroke *[see Contraindications (4.2)]*. The treatment effect was driven primarily by a reduction in nonfatal MI. The effect in patients ≥75 years of age was also somewhat smaller, and bleeding risk is higher in these individuals *[see Adverse Reactions (6.1)]*. See below for analyses of patients ≥75 years of age with risk factors.

Baseline Characteristics		N	Percent Events	
			Effient	Clopidogrel
OVERALL-UA/NSTEMI		10074	9.9	12.1
Age	<65 y	5987	7.6	10.0
	≥65 y	4087	11.9	13.1
	<75 y	8672	8.2	10.5
	≥75 y	1402	15.8	16.2
Gender	Female	2724	10.3	11.4
	Male	7350	8.9	11.2
Body Weight	<60 kg	503	9.2	9.8
	≥60 kg	9458	9.2	11.1
Region	North America	3538	9.6	11.9
	United States	3382	9.7	12.2
	South America	534	13.3	15.2
	Western Europe	2527	8.8	9.8
	Eastern Europe	2300	8.5	10.0
	Rest of World	1175	9.1	13.1
Diabetes Mellitus	Yes	2472	10.8	15.0
	No	7602	8.8	10.0
Metabolic Syndrome	Yes	4511	9.1	11.5
	No	5563	9.6	11.1
Previous MI	Yes	2075	12.9	15.8
	No	7999	8.3	10.1
Previous PCI	Yes	1597	12.0	14.8
	No	8477	8.8	10.6
Previous CABG	Yes	957	16.0	18.2
	No	9117	8.6	10.5
Previous TIA/Stroke	Yes	405	18.3	12.5
	No	9669	8.9	11.2
Time From Symptom Onset	≤24 h	3902	8.3	10.8
	>24 h	5976	10.1	11.5
Stent Type	Drug-eluting ≥1	5225	9.2	10.9
	Bare Metal Only	4362	9.2	11.6
	None	401	11.7	14.9
GP IIb/IIIa Inhibitor Use	Yes	5183	9.9	11.9
	No	4891	8.7	10.5

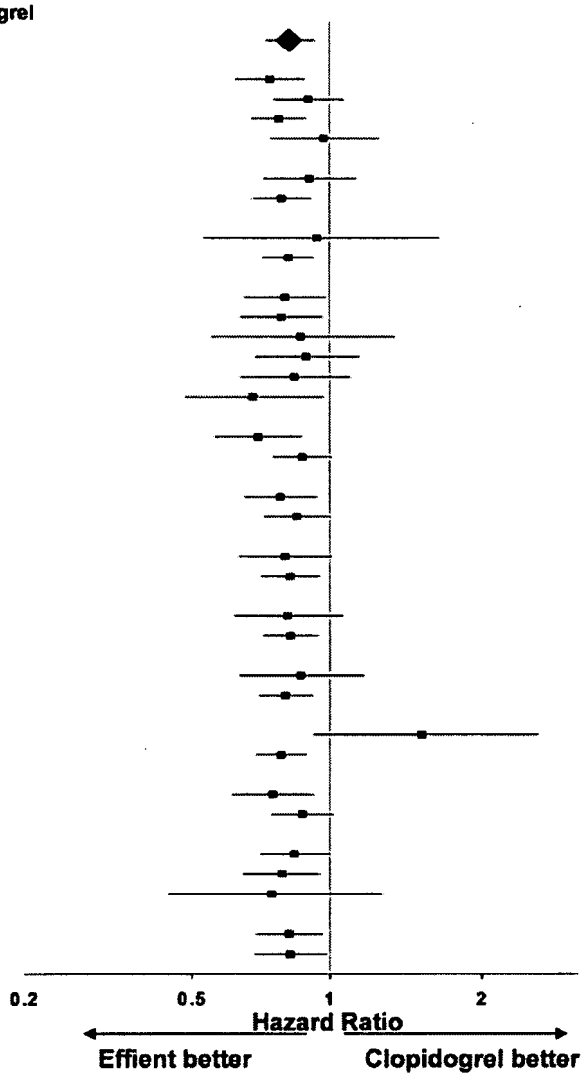


Figure 4: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – UA/NSTEMI Patients.

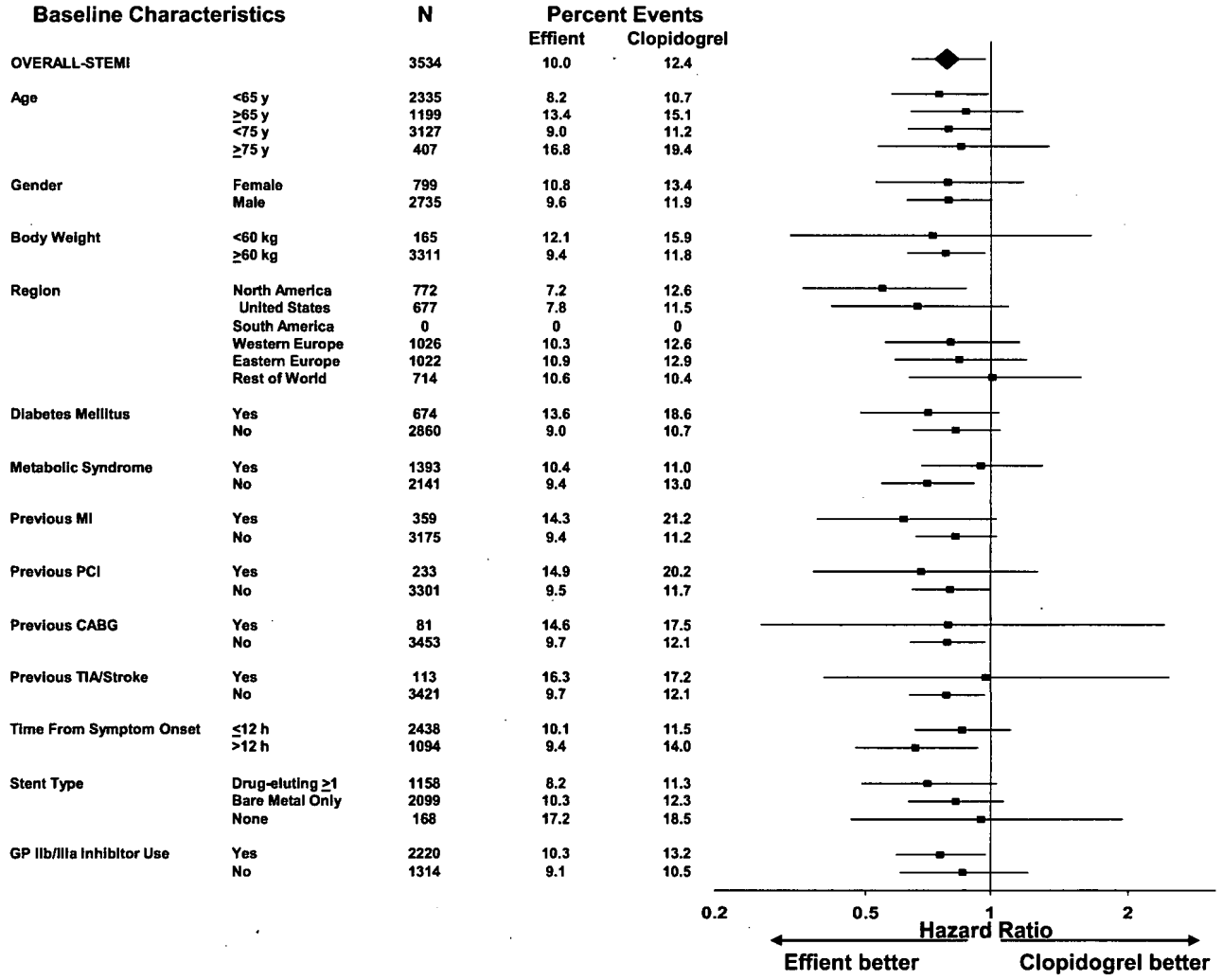


Figure 5: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – STEMI Patients.

Effient is generally not recommended in patients ≥75 years of age, except in high-risk situations (diabetes mellitus or prior MI) where its effect appears to be greater and its use may be considered. These recommendations are based on subgroup analyses (Table 6) and must be interpreted with caution, but the data suggest that Effient reduces ischemic events in such patients.

Table 6: Subgroup Analyses for Time to First Event of CV Death, MI, or Stroke: Patients < or ≥75 Years of Age, ± Diabetes, ± Prior History of MI, All ACS Patient Population

	Effient		Clopidogrel			
	N	% with events	N	% with events	Hazard Ratio (95% CI)	p-value
Age ≥75						
Diabetes - yes	249	14.9	234	21.8	0.64 (0.42, 0.97)	0.034
Diabetes - no	652	16.4	674	15.3	1.1 (0.83, 1.43)	NS
Age <75						
Diabetes - yes	1327	10.8	1336	14.8	0.72 (0.58, 0.89)	0.002
Diabetes - no	4585	7.8	4551	9.5	0.82 (0.71, 0.94)	0.004
Age ≥75						
Prior MI - yes	220	17.3	212	22.6	0.72 (0.47, 1.09)	0.12
Prior MI - no	681	15.6	696	15.2	1.05 (0.80, 1.37)	NS
Age <75						

Prior MI - yes	1006	12.2	996	15.4	0.78 (0.62, 0.99)	0.04
Prior MI - no	4906	7.7	4891	9.7	0.78 (0.68, 0.90)	<0.001

There were 50% fewer stent thromboses (95% C.I. 32% - 64%; p< 0.001) reported among patients randomized to Effient (0.9%) than among patients randomized to clopidogrel (1.8%). The difference manifested early and was maintained through one year of follow-up. Findings were similar with bare metal and drug-eluting stents.

In TRITON-TIMI 38, prasugrel reduced ischemic events (mainly nonfatal MIs) and increased bleeding events *[see Adverse Reactions (6.1)]* relative to clopidogrel. The findings are consistent with the intended greater inhibition of platelet aggregation by prasugrel at the doses used in the study *[see Clinical Pharmacology (12.2)]*. There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel's active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel's active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. Moreover, certain proton pump inhibitors, widely used in the ACS patient population and used in TRITON-TIMI 38, inhibit CYP2C19, thereby decreasing formation of clopidogrel's active metabolite. Thus, reduced metabolizer status and use of proton pump inhibitors may diminish clopidogrel's activity in a fraction of the population, and may have contributed to prasugrel's greater treatment effect and greater bleeding rate in TRITON-TIMI 38. The extent to which these factors were operational, however, is unknown.

16 HOW SUPPLIED/STORAGE AND HANDLING

Effient (prasugrel) 5 mg is supplied as a yellow, elongated hexagonal, film-coated, non-scored tablet debossed with "5 MG" on one side and with "4760" on the other side.

5 mg tablets are supplied as follows:

Bottles of 7 - NDC 0002-4760-76

Bottles of 30 - NDC 0002-4760-30

Effient (prasugrel) 10 mg is supplied as a beige, elongated hexagonal, film-coated, non-scored tablet debossed with "10 MG" on one side and "4759" on the other side.

10 mg tablets are supplied as follows:

Bottles of 30 – NDC 0002-4759-30

Blisters ID 90* NDC 0002-4759-77

(*Identi Dose®, unit dose medication, Lilly)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Dispense and keep product in original container. Keep container closed and do not remove desiccant from bottle. Do not break the tablet.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 Benefits and Risks

- Summarize the effectiveness features and potential side effects of Effient.
- Tell patients to take Effient exactly as prescribed.
- Remind patients not to discontinue Effient without first discussing it with the physician who prescribed Effient.
- Recommend that patients read the Medication Guide.

17.2 Bleeding

Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with medications in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

17.4 Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking Effient before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping Effient.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (*e.g.*, warfarin and NSAIDs).

Literature Issued:

490 **Manufactured by Eli Lilly and Company, Indianapolis, IN, 46285**

491 **Marketed by Daiichi Sankyo, Inc. and Eli Lilly and Company**

493 A 12.0 NL 6107 AMP PRINTED IN USA

EXHIBIT 3
APPROVAL LETTER FOR EFFIENT™

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-307

NDA APPROVAL

Eli Lilly and Company
Attention: Elizabeth C. Bearby, Pharm.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Bearby:

Please refer to your new drug application (NDA) dated December 26, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Effient (prasugrel) 5 and 10 mg Tablets.

We acknowledge receipt of your submissions dated January 9, 15, 25, 28 and 30, February 4, 6, 19, 25 and 28, March 20 (two), 21, 24, 25 and 28, April 2, 7 (two), 14, 15, 17, 22 (two), 24 (two), 25, 28 and 30 (three), May 6, 9 (two), 10, 12 (two), 14, and 16, June 11 (two), 17, 20 (two) and 25 (two), July 22 and 30, August 8, 14, 19, 25 and 28, September 4, 11, 18, 22, 24 and 26, October 3 (two), 10 (two) and 23, November 4, 12, 13, 17 and 21, December 3, 5, 11, 12, 18 (two) and 23, 2008, and January 1, 5, 7, 15, 19, 20, 27 (two) and 29, February 6, 12, 13, 19 and 23, March 5, 10 (two), 11, 12, 13 and 23, April 24, May 4, 21 and 22, June 4, 10, 12, 13, and 25, July 8 (two), 9 (three), 2009.

This new drug application provides for the use of Effient (prasugrel) 5 and 10 mg Tablets for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI)
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to enclosed labeling (text for the package insert, and Medication Guide). Upon receipt, we will transmit that version to the

National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "**SPL for approved NDA 22-307**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-307**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Cardiovascular and Renal Products do not object to the use of the proprietary name Effient for this product.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application. The studies needed to assess the value of Effient in acute coronary syndrome in children would be impossible to conduct because the disease does not exist in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct post-marketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of major bleeding and a signal of a serious risk of increased incidence of malignancies.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a non-clinical or observational study) will be sufficient to assess this known risk of bleeding and signal of risk of increased malignancies. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. An open-label trial of *ex vivo* reversal of platelet inhibition by exogenous platelets as a function of time and plasma level of prasugrel active metabolite in 28 normal volunteers administered a single 60-mg loading dose of prasugrel plus aspirin 325 mg. The methods should be similar to those described by Vilahur *et. al.,* 2007. J. Thromb Haemost 5:82. Descriptive statistics should be reported.

   The timetable you submitted on July 8, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	09/2009
Trial Completion Date:	08/2011
Final Report Submission:	09/2011

2. You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449.

   The timetable you submitted on July 8, 2009 states that you will conduct this trial according to the following timetable:

Protocol Submission:	06/2008
Trial Completion Date:	12/2012
Final Report Submission:	01/2013

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any post-marketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of your post-marketing commitments in your submission dated July 10, 2009. These commitments are listed below:

3. You commit to develop a new formulation of the Effient (prasugrel) drug product that (b) (4) . You commit to submit the data to support this new formulation as a supplemental new drug application (sNDA). The submission will provide information on the development, manufacture, control, and stability of the new formulation. In addition, you commit to develop a robust and sensitive method to quantify very low level (b) (4) in the reformulated product, and submit this information to the sNDA.

   sNDA Submission Date: (b) (4)

4. You commit to performing a clinical trial in the fasting and fed state, to compare the pharmacokinetics of single 60-mg doses of the marketed and new prasugrel formulations with respect to concentrations of the prasugrel active metabolite and effects on platelet inhibition.

   We understand that the protocols for these trials have been submitted.

   Trial Completion Date: 08/2009
   Final Report Submission: 12/2009

5. You commit to performing, in the presence and absence of a proton pump inhibitor, a clinical trial to compare the pharmacodynamics of single 60-mg doses of the marketed and new prasugrel formulations with respect to concentrations of the prasugrel active metabolite and effects on platelet inhibition.

We understand that the protocols for these trials have been submitted and the trial has been completed.

Final Report Submission: 12/2009

6. You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing.

   We understand that the protocols for these trials have been submitted.

   Trial Completion Date: 12/2012
   Final Report Submission: 01/2013

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these post-marketing study commitments should be prominently labeled "**Post-marketing Study Commitment Protocol,**" "**Post-marketing Study Commitment Final Report,**" or "**Post-marketing Study Commitment Correspondence.**"

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on July 10, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, an implementation system, and a timetable for submission of assessments of the REMS.

The information needed for assessment (REMS Assessment Plan) should include the following data:

- Patients' understanding of the serious risks of Effient (prasugrel)
- Patients' understanding, via a patient survey, of the Medication Guides

- A report on periodic assessments of the distribution and dispensing of the Introductory Letter and Prescriber Brochure.
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address non-compliance.
- Prescribers' understanding, via a prescriber's survey, of the safety messages and adherence to the boxed warning.
- A description of specific measures that would be taken to increase awareness if surveys of healthcare prescribers indicate that prescriber awareness is not adequate.

You are expected to submit a detailed description of methodology and the instruments used in the prescriber and patient surveys. A complete description of survey protocols is to be submitted to FDA 90 days prior to conducting surveys. The survey protocol submission should include:

- The sample size and confidence interval associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of prescribers/patients surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- An explanation of controls used to minimize bias
- An explanation of controls used to compensate for the limitations associated with their methodology
- An explanation of what will be done with the resulting data from the surveys
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and the correlation to the messages in the Medication Guide.

The requirements for assessments of an approved REMS also include, in section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-307 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-307
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22-307
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

PRODUCT EXPIRATION

An expiration dating period of 18 month is granted for Effient tablets, 5 and 10 mg stored in bottles at 25°C (USP Controlled Room Temperature). Effient 10 mg tablets stored in blisters will have an expiration dating period of 12 months.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package inserts to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (*i.e.*, a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call:

Meg Pease-Fye, M.S., R.A.C.
Regulatory Project Manager
(301) 796 - 1130

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Final Product Labeling
REMS
Medication Guide
Introductory Letter
Prescriber's Brochure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
7/10/2009 02:33:24 PM

EXHIBIT 4
PATENT (USP 5,288,726)

US005288726A

United States Patent [19]

Koike et al.

[11] Patent Number: 5,288,726

[45] Date of Patent: Feb. 22, 1994

[54] **TETRAHYDROTHIENOPYRIDINE DERIVATIVES, FURO AND PYRROLO ANALOGS THEREOF AND THEIR PREPARATION AND USES FOR INHIBITING BLOOD PLATELET AGGREGATION**

[75] Inventors: **Hiroyuki Koike; Fumitoshi Asai; Atsuhiro Sugidachi**, all of Tokyo; **Tomio Kimura**, Ube; **Teruhiko Inoue**, Ube; **Shigeyoshi Nishino**, Ube; **Yasunori Tsuzaki**, Ube, all of Japan

[73] Assignees: **Ube Industries Limited**, Ube; **Sankyo Company, Limited**, Tokyo, both of Japan

[21] Appl. No.: **941,676**

[22] Filed: **Sep. 8, 1992**

[30] **Foreign Application Priority Data**

Sep. 9, 1991 [JP] Japan 3-227875
May 29, 1992 [JP] Japan 4-138529

[51] **Int. Cl.**[5] **A01K 3/14; C07D 513/04**
[52] **U.S. Cl.** **514/301**; 546/114
[58] **Field of Search** 546/114, 116; 514/301, 514/302

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,051,141	9/1977	Castaigne	260/294.8
4,075,215	2/1978	Castaigne	260/294.8
4,127,580	11/1978	Braye	546/114
4,136,186	1/1979	Frehel et al.	546/114
4,458,074	7/1984	Bouscuet et al.	546/114
4,464,377	8/1984	Blanchard et al.	424/256
4,529,596	7/1985	Aubert et al.	514/231
4,740,510	4/1988	Badorc et al.	514/291

FOREIGN PATENT DOCUMENTS

421861 4/1991 European Pat. Off. 546/114

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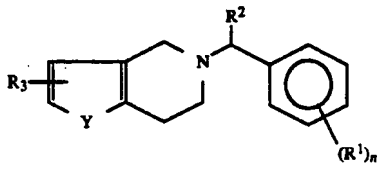
Attorney, Agent, or Firm—Frishauf, Holtz, Goodman & Woodward

[57] **ABSTRACT**

Compounds of formula (I):



(I)

wherein: R^1 is hydrogen, alkyl, halogen, haloalkyl, hydroxy, alkoxy, haloalkoxy, alkylthio, haloalkylthio, amino, alkanoyl, haloalkanoyl, carboxy, alkoxycarbonyl, carbamoyl, cyano, nitro, alkanesulfonyl, haloalkanesulfonyl or sulfamoyl; R^2 is optionally substituted alkanoyl, optionally substituted alkenoyl, optionally substituted cycloalkylcarbonyl, substituted benzoyl, or 5,6-dihydro-1,4,2-dioxazin-3-yl; R^3 is hydrogen, hydroxy, optionally substituted alkoxy, aralkyloxy, alkanoyloxy, alkenoyloxy, cycloalkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aralkyloxycarbonylxy, phthalidyloxy, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy, optionally substituted amino or nitro; Y is —NH— or oxygen or sulfur; n is 1 to 5; and tautomers and salts of said compounds of formula (I), have the ability to inhibit blood platelet aggregation, and can thus be used for treatment and prophylaxis of thrombosis and embolisms.

56 Claims, No Drawings

TETRAHYDROTHIENOPYRIDINE DERIVATIVES, FURO AND PYRROLO ANALOGS THEREOF AND THEIR PREPARATION AND USES FOR INHIBITING BLOOD PLATELET AGGREGATION

BACKGROUND OF THE INVENTION

The present invention relates to a series of new tetrahydrothieno[3,2-c]pyridine derivatives and furo and pyrrolo analogs of these derivatives, and provides processes for preparing these derivatives as well as methods and compositions using them for inhibiting blood platelet aggregation.

A number of tetrahydrothienopyridine and tetrahydrofuropyridine derivatives is known, and some of these have been disclosed to have the ability to inhibit blood platelet aggregation. For example, U.S. Pat. Nos. 4,051,141, 4,075,215, 4,127,580, 4,464,377 and 4,529,596 all disclose compounds of this type, although not all disclose them for the inhibition of blood platelet aggregation. The closest prior art is believed to be U.S. Pat. No. 4,051,141, which discloses, inter alia, 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and U.S Pat. No. 4,529,596, which discloses, inter alia, 5-(2-chloro-α-methoxycarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

However, there are problems with the prior art compounds referred to above, especially in that many of them require a long time after administration before they manifest their activity. Accordingly, there is a need for new compounds of this type having improved activity and the ability to act faster.

We have now discovered a series of new tetrahydrothieno[3,2-c]pyridine derivatives and furo and pyrrolo analogs of these derivatives which have an improved ability to inhibit the aggregation of blood platelets.

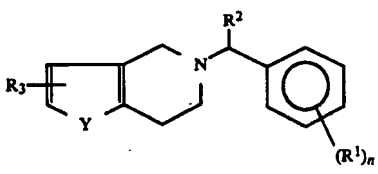
BRIEF SUMMARY OF INVENTION

It is, therefore, an object of the present invention to provide a series of new compounds of this type.

It is a further, and more specific object of the present invention to provide such compounds having valuable inhibitory activity against platelet aggregation.

Other objects and advantages of the present invention will become apparent as the description proceeds.

The compounds of the present invention are those compounds of formula (I):



(I)

wherein:

R^1 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halogen atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 1 to 10 carbon atoms, a substituted alkanoyl group which has from 2 to 10 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below, an alkenoyl group having from 3 to 6 carbon atoms, a substituted alkenoyl group which has from 3 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below, a cycloalkylcarbonyl group having from 4 to 8 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 8 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below, a substituted benzoyl group having at least one substituent selected from the group consisting of substituents B, defined below, or a 5,6-dihydro 1,4,2-dioxazin-3-yl group;

R^3 represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a substituted alkoxy group which has from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents C, defined below, an aralkyloxy group in which the aralkyl part is as defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having from 3 to 6 carbon atoms, a cycloalkyl carbonyloxy group having from 4 to 8 carbon atom, an arylcarbonyloxy group in which the aryl part is as defined below, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, an aralkyloxycarbonyloxy group in which the aralkyl part is as defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula $-NR^aR^b$

wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, alkyl groups having from 1 to 4 carbon atoms and substituted alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one substituent selected from the group consisting of substituents C, defined below,

an aralkylamino group in which the aralkyl part is as defined below, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamin group having from 3 to 6 carbon atoms, a cycloalkylcarbonylamino group having from 4 to 8 carbon atoms, an arylcarbonylamino group in which the aryl part is as defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms, an aralkyloxycarbonylamino group in which the aralkyl part is as defined below, a phthalidylamino group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylamino group, a (5-phenyl-2-

oxo-1,3-dioxolen-4-yl)methylamino group or a nitro group;

Y represents a group of formula —NH— or an oxygen or sulfur atom; and

n is an integer from 1 to 5, and, when n is an integer from 2 to 5, the groups represented by R^1 may be the same as or different from each other;

said substituents A are selected from the group consisting of halogen atoms, hydroxy groups, alkoxy groups having from 1 to 4 carbon atoms and cyano groups;

said substituents B are selected from the group consisting of alkyl groups having from 1 to 4 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms;

said substituents C are selected from the group consisting of alkoxy groups having from 1 to 4 carbon atoms, alkanoyloxy groups having from 1 to 6 carbon atoms and arylcarbonyloxy groups in which the aryl part is as defined below;

said aralkyl parts of said aralkyloxy, aralkyloxy. carbonyloxy, aralkylamino and aralkyloxycarbonylamino groups are alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one aryl group as defined below;

said aryl groups and said aryl parts of said arylcarbonyloxy groups and of said arylcarbonylamino groups have from 6 to 10 carbon atoms in a carbocyclic ring which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D, defined below; and

said substituents D are selected from the group consisting of the groups and atoms defined above in relation to R^1, other than said hydrogen atom;

and tautomers thereof and pharmaceutically acceptable salts of said compounds of formula (I) and of said tautomers.

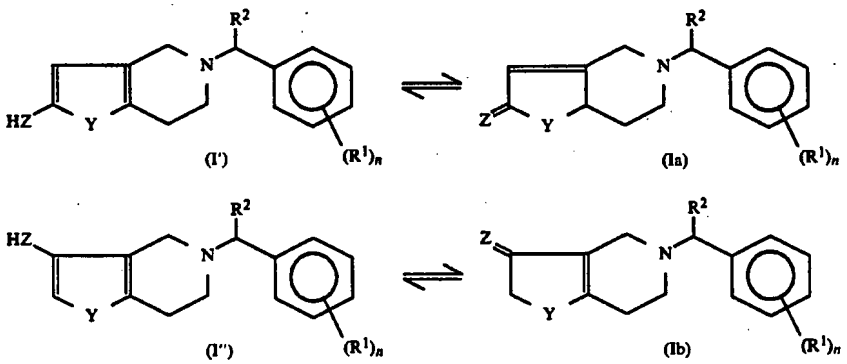
The invention also provides a pharmaceutical composition for the treatment and prophylaxis of thrombosis or embolisms, comprising an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof.

The invention still further provides a method for the treatment or prophylaxis of thrombosis or embolisms, comprising administering to a mammal, which may be human, an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof.

The invention also provides processes for preparing these compounds, which are described in greater detail hereafter.

DETAILED DESCRIPTION OF INVENTION

When the compounds of the present invention have an amino or hydroxy group at the 2- or 3- position (i.e. R^3 represents an amino or hydroxy group at the 2- or 3-position), they can exist as keto-enol tautomers, that is:



wherein Y, R^1, R^2 and n are as defined above, and Z represents a group of formula =NH or an oxygen tom. These tautomers may or may not be readily separable, and, if separable, may be separated by methods well known in the art. In any event, the present invention embraces both the individual isolated tautomers, as well as mixtures thereof, and both the isolated tautomers and such mixtures may be used in the compositions and methods of the present invention. In particular, the tautomers of formula (Ia) are preferred.

In the compounds of the present invention, where R^1 represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 4 carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and t-butyl groups. Of these, we prefer those alkyl groups having from 1 to 3 carbon atoms, more preferably the methyl and ethyl groups.

Where R^1 represents a halogen atom, this may be, for example, a fluorine, chlorine, iodine or bromine atom, and is preferably a fluorine or chlorine atom.

Where R^1 represents a haloalkyl group, the alkyl part may be any one of the alkyl groups exemplified above and may be substituted by one or more halogen (for example fluorine, chlorine, bromine or iodine) atoms. There is, in principle, no restriction on the number of halogen substituents on the alkyl group, this being limited only by the number of substitutable atoms. In general, however, from 1 to 5 halogen substituents are preferred, from 1 to 3 substituents being more preferred. Specific examples of such groups include the fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2-fluoropropyl, 3-fluoropropyl, 3-chloropropyl, 2-fluorobutyl, 3-fluorobutyl, 4-chlorobutyl and 4-fluorobutyl groups. The fluorine-substituted and chlorine-substituted groups are preferred, the fluorine-substituted groups being more preferred. The fluoromethyl, difluoromethyl and trifluoromethyl

groups are most preferred, especially the trifluoromethyl group.

Where R^1 represents an alkoxy group, this may be a straight or branched chain alkoxy group having from 1 to 4 carbon atoms, and examples include the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and t-butoxy groups. Of these, we prefer those alkoxy groups having from 1 to 3 carbon atoms, more preferably the methoxy and ethoxy groups.

Where R^1 represents a haloalkoxy group, the alkoxy part may be any one of the alkoxy groups exemplified above and may be substituted by one or more halogen (for example fluorine, chlorine, bromine or iodine) atoms. There is, in principle, no restriction on the number of halogen substituents on the alkoxy group, this being limited only by the number of substitutable atoms. In general, however, from 1 to 5 halogen substituents are preferred, from 1 to 3 substituents being more preferred. Specific examples of such groups include the fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 2-iodoethoxy, 2,2,2-trichloroethoxy, 2,2,2-trifluoroethoxy, 2-fluoropropoxy, 3-fluoropropoxy, 3-chloropropoxy, 2-fluorobutoxy, 3-fluorobutoxy, 4-chlorobutoxy and 4-fluorobutoxy groups. The fluoroalkoxy groups are preferred. The fluoromethoxy, difluoromethoxy and trifluoromethoxy groups are most preferred, especially the trifluoromethoxy group.

Where R^1 represents an alkylthio group, this may be a straight or branched chain alkylthio group having from 1 to 4 carbon atoms, and examples include the methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio and t-butylthio groups. Of these, we prefer those alkylthio groups having from 1 to 3 carbon atoms, more preferably the methylthio and ethylthio groups.

Where R^1 represents a haloalkylthio group, the alkylthio part may be any one of the alkylthio groups exemplified above and may be substituted by one or more halogen (for example fluorine, chlorine, bromine or iodine) atoms. There is, in principle, no restriction on the number of halogen substituents on the alkylthio group, this being limited only by the number of substitutable atoms. In general, however, from 1 to 5 halogen substituents are preferred, from 1 to 3 substituents being more preferred. Specific examples of such groups include the fluoromethylthio, difluoromethio, trifluoromethylthio, 2-fluoroethylthio, 2-chloroethylthio, 2-bromoethylthio, 2-iodoethylthio, 2,2,2-trichloroethylthio, 2,2,2-trifluoroethylthio, 2-fluoropropylthio, 3-fluoropropylthio, 3-chloropropylthio, 2-fluorobutylthio, 3-fluorobutylthio, 4-chlorobutylthio and 4-fluorobutylthio groups. The fluorine substituted groups are preferred. The fluoromethylthio, difluoromethylthio and trifluoromethylthio groups are most preferred, especially the trifluoromethylthio group.

Where R^1 represents an alkanoyl group, this has from 1 to 5 carbon atoms and may be a straight or branched chain group. Examples include the formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl and pivaloyl groups, of which the formyl and acetyl groups are preferred.

Where R^1 represents a haloalkanoyl group, this has from 2 to 5 carbon atoms and may be a straight or branched chain group. Examples include the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, trichloroacetyl, bromoacetyl, iodoacetyl, 3-fluoropropionyl, 4-fluorobutyryl and 5-fluorovaleryl groups. Of these, the fluorine substituted alkanoyl groups are preferred, the fluoroacetyl, difluoroacetyl and trifluoroacetyl groups being more preferred and the trifluoroacetyl group being most preferred.

Where R^1 represents an alkoxycarbonyl group, this may be a straight or branched chain alkoxycarbonyl group having from 2 to 5 carbon atoms, that is the alkoxy part has from 1 to 4 carbon atoms, and examples include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl and t-butoxycarbonyl groups. Of these, we prefer those alkoxycarbonyl groups having from 1 to 3 carbon atoms, more preferably the methoxycarbonyl and ethoxycarbonyl groups.

Where R^1 represents an alkanesulfonyl group, this may be a straight or branched chain alkanesulfonyl group having from 1 to 4 carbon atoms, and examples include the methanesulfonyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, isobutanesulfonyl, sec butanesulfonyl and t-butanesulfonyl groups. Of these, we prefer those alkanesulfonyl groups having from 1 to 3 carbon atoms, more preferably the methanesulfonyl and ethanesulfonyl groups.

Where R^1 represents a haloalkanesulfonyl group, the alkanesulfonyl part may be any one of the alkanesulfonyl groups exemplified above and may be substituted by one or more halogen (for example fluorine, chlorine, bromine or iodine) atoms. There is, in principle, no restriction on the number of halogen substituents on the alkanesulfonyl group, this being limited only by the number of substitutable atoms. In general, however, from 1 to 5 halogen substituents are preferred, from 1 to 3 substituents being more preferred. Specific examples of such groups include the fluoromethanesulfonyl, difluoromethanesulfonyl, trifluoromethanesulfonyl, dichloromethanesulfonyl, trichloromethanesulfonyl, 2-fluoroethanesulfonyl, 2-chloroethanesulfonyl 2-bromoethanesulfonyl, 2-iodoethanesulfonyl, 2,2,2-trichloroethanesulfonyl, 2,2,2-trifluoroethanesulfonyl, 2-fluoropropanesulfonyl, 3-fluoropropanesulfonyl, 3-chloropropanesulfonyl, 2-fluorobutanesulfonyl, 3-fluorobutanesulfonyl, 4-chlorobutanesulfonyl and 4-fluorobutanesulfonyl groups. The fluorine-substituted alkanesulfonyl and chlorine substituted alkanesulfonyl groups are preferred, the fluorine-substituted alkanesulfonyl groups being more preferred. The fluoromethanesulfonyl, difluoromethanesulfonyl and trifluoromethanesulfonyl groups are most preferred, especially the trifluoromethanesulfonyl group.

Of the above groups and atoms, we especially prefer that R^1 should represent: a hydrogen atom; an alkyl group having from 1 to 4 carbon atoms; a halogen atom; a fluorine substituted alkyl group having from 1 to 4 carbon atoms; a hydroxy group; an alkoxy group having from 1 to 4 carbon atoms; a fluorine-substituted alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; a fluorine-substituted alkylthio group having from 1 to 4 carbon atoms; an amino group; an alkanoyl group having from 1 to 5 carbon atoms; a fluorine-substituted alkanoyl group having from 2 to 5 carbon atoms; an alkoxycarbonyl group having from 2 to 5 carbon atoms; a carbamoyl group; a cyano group; a nitro group; an alkanesulfonyl group having from 1 to 4 carbon atoms; a fluorine-substituted alkanesulfonyl group having from 1 to 4 carbon atoms; or a sulfamoyl group.

More preferably R^1 represents: a hydrogen atom; a methyl group; an ethyl group; a halogen atom; a fluo-

rine-substituted methyl group; a hydroxy group; a methoxy group; an ethoxy group; a fluorine-substituted methoxy group; a methylthio group; a fluorine-substituted methylthio group; a formyl group; an acetyl group; a fluorine-substituted acetyl group; a methoxycarbonyl group; an ethoxycarbonyl group; a propoxycarbonyl group; a carbamoyl group; a cyano group; a nitro group; a methanesulfonyl group; an ethanesulfonyl group; a fluorine-substituted methanesulfonyl group; or a sulfamoyl group.

Still more preferably R^1 represents: a halogen atom; a trifluoromethyl group; a hydroxy group; a difluoromethoxy group; a trifluoromethoxy group; a difluoromethylthio group; a trifluoromethylthio group; a formyl group; an acetyl group; a trifluoroacetyl group; a cyano group or a nitro group.

Most preferably R^1 represents: a fluorine atom, a chlorine atom or a trifluoromethyl group; especially a fluorine atom or a chlorine atom.

The number of the substituents, n, represented by R^1 is from 1 to 5, although the maximum may be lower than 5 in some cases if there is a problem of steric hindrance. Preferably n is from 1 to 3, and more preferably 1 or 2. The position of substitution by R^1 on the phenyl group is preferably para or ortho, more preferably ortho.

Where R^2 represents an alkanoyl group having from 1 to 10 carbon atoms, this may be a straight or branched chain group, and examples include the formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl and decanoyl groups, of which those groups having from 2 to 6 carbon atoms are preferred, especially the acetyl, propionyl and isobutyryl groups, of which the acetyl and propionyl groups are most preferred.

Those alkanoyl groups represented by R^2 and having from 2 to 10 carbon atoms may be substituted by one or more of substituents A, defined above. Examples of such substituents A include:

- halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms;
- hydroxy groups;
- alkoxy groups having from 1 to 4 carbon atoms, such as those exemplified above in relation to R^1; and
- cyano groups.

In the case of these substituted groups, and all substituted groups referred to herein, there is no specific limitation on the number of the substituents, except such as may be imposed by the number of substitutable positions and possibly also by steric constraints. However, in general, from 1 to 3 such substituents are preferred.

Specific examples of such substituted alkanoyl groups include the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, trichloroacetyl, bromoacetyl, iodoacetyl, 3-fluoropropionyl, 3-cloropropionyl, 3-bromopropionyl, 3-iodopropionyl, 4-fluorobutyryl, 4-chlorobutyryl, 5-fluorovaleryl, hydroxyacetyl, 3-hydroxypropionyl, 4-hydroxybutyryl, 5-hydroxyvaleryl, methoxyacetyl, 3-methoxypropionyl, 4-methoxybutyryl, 5-methoxyvaleryl, ethoxyacetyl, 3-ethoxypropionyl, 4-ethoxybutyryl, 5-ethoxyvaleryl, cyanoacetyl, 3-cyanopropionyl, 4-cyanobutyryl and 5-cyanovaleryl groups, of which the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, 3-fluoropropionyl, 3-chloropropionyl, hydroxyacetyl, 3-hydroxypropionyl, methoxyacetyl, 3-methoxypropionyl, ethoxyacetyl, cyanoacetyl and 3-cyanopropionyl groups are more preferred. Still more preferred are the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, 3-fluoropropionyl, hydroxyacetyl, methoxyacetyl, ethoxyacetyl and cyanoacetyl groups. The most preferred groups are the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, 3-fluoropropionyl, hydroxyacetyl, methoxyacetyl and cyanoacetyl groups, especially the fluoroacetyl, difluoroacetyl and trifluoroacetyl groups.

Where R^2 represents an alkenoyl group having from 3 to 6 carbon atoms, this may be a straight or branched chain group, and examples include the acryloyl, methacryloyl, 2-butenoyl, 2-pentenoyl and 2-hexenoyl groups, of which the acryloyl and methacryloyl groups are preferred.

These alkenoyl groups may also be substituted by one or more of substituents A, defined and exemplified above. Specific examples of such substituted groups include the 3-fluoroacryloyl, 3-chloroacryloyl and 3-cyanoacryloyl groups, of which the 3-fluoroacryloyl group is particularly preferred.

Where R^2 represents a cycloalkylcarbonyl group, this has from 4 to 8 carbon atoms, that is the cycloalkyl group itself has from 3 to 7 ring carbon atoms. Examples of such groups include the cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexyl carbonyl and cycloheptylcarbonyl groups, of which the cyclopropylcarbonyl and cyclobutylcarbonyl groups are particularly preferred.

These cycloalkylcarbonyl groups may also be substituted by one or more of substituents A, defined and exemplified above. Specific examples of such substituted groups include the 2-fluorocyclopropylcarbonyl, 2,2-difluorocyclopropylcarbonyl, 2-chlorocyclopropylcarbonyl, 2-bromocyclopropylcarbonyl, 2-fluorocyclobutylcarbonyl, 2-chlorocyclobutylcarbonyl, 2-fluorocyclopentylcarbonyl, 2-chlorocyclopentyl carbonyl, 2-fluorocyclohexylcarbonyl, 2-chlorocyclohexylcarbonyl, 2-hydroxycyclopropylcarbonyl, 2-hydroxycyclobutylcarbonyl, 2-hydroxycyclopentylcarbonyl, 2-hydroxycyclohexylcarbonyl, 2-methoxycyclopropylcarbonyl, 2-methoxycyclobutylcarbonyl, 2-methoxycyclopentylcarbonyl, 2-methoxycyclohexylcarbonyl, 2-ethoxycyclopropylcarbonyl, 2-ethoxycyclobutylcarbonyl, 2-ethoxycyclopentylcarbonyl, 2-ethoxycyclohexylcarbonyl, 2-cyanocyclopropylcarbonyl, 2-cyanocyclobutylcarbonyl, 2-cyanocyclopentylcarbonyl and 2-cyanocyclohexylcarbonyl groups, of which the 2-fluorocyclopropylcarbonyl, 2,2-difluorocyclopropylcarbonyl, 2-chlorocyclopropylcarbonyl, 2-fluorocyclobutylcarbonyl, 2-chlorocyclobutylcarbonyl, 2 fluorocyclopentylcarbonyl, 2-fluorocyclohexylcarbony, 2-hydroxycyclopropylcarbonyl, 2-methoxycyclopropylcarbonyl, 2-ethoxycyclopropyl. carbonyl and 2-cyanocyclopropylcarbonyl groups are preferred. More preferred groups are the 2-fluorocyclopropylcarbonyl, 2-chlorocyclopropylcarbonyl, 2-fluorocyclobutylcarbonyl and 2-methoxycyclopropyl carbonyl groups, and the most preferred is the 2-fluorocyclopropylcarbonyl group.

Where R^2 represents a substituted benzoyl group, this is substituted by at least one of substituents B, which are selected from the group consisting of alkyl groups having from 1 to 4 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms, all of which may be as exemplified in relation to the same groups and atoms represented by R^1. The number of the substituents may be from 1 to 5, provided that there is no problem of steric hindrance; preferably, however, are from 1 to 3 substituents, more preferably 1 or Specific exam-

ples of such substituted benzoyl groups include the 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2,4-difluorobenzoyl, 2,4,6-trifluorobenzoyl, 2,3,4,5,6-pentafluorobenzoyl, 4-chlorobenzoyl, 2,4-dichlorobenzoyl, 4-methylbenzoyl, 2,4-dimethylbenzoyl, 4-ethylbenzoyl, 2,4-diethylbenzoyl, 4-methoxybenzoyl, 2,4-dimethoxybenzoyl, 4-ethoxybenzoyl and 2,4-diethoxybenzoyl groups, of which the 4-fluorobenzoyl and 2,4-difluorobenzoyl groups are preferred.

Where R^3 represents an alkoxy group, this may be a straight or branched chain group having from 1 to 4 carbon atoms and may be any of the alkoxy groups exemplified above in relation to R^1. Such a group may be unsubstituted or it may have one or more substituents selected from the group consisting of substituents C, defined above, and examples of which are as follows:

- alkoxy groups having from 1 to 4 carbon atoms, such as those exemplified above in relation to R^1;
- alkanoyloxy groups having from 1 to 6 carbon atoms, which may be a straight or branched chain group, for example the formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy or hexanoyloxy groups, of which those groups having from 1 to 5 carbon atoms are preferred, and the acetoxy, propionyloxy, butyryloxy and pivaloyloxy groups are most preferred; and
- arylcarbonyloxy groups in which the aryl part is as defined above, for example the arylcarbonyloxy groups exemplified below in relation to R^3.

Specific examples of such substituted alkoxy groups include the methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, formyloxymethoxy, acetoxymethoxy, propionyloxymethoxy, 2-formyloxyethoxy, 2-acetoxyethoxy, 2-propionyloxyethoxy, 3-acetoxypropoxy, 4-acetoxybutoxy, valeryloxymethoxy, pivaloyloxymethoxy, benzoyloxymethoxy, naphthoyloxymethoxy, p-toluoyloxymethoxy, p-chlorobenzoyloxymethoxy, 2-benzoyloxyethoxy, 3-benzoyloxypropoxy and 4-benzoyloxybutoxy groups, of which the pivaloyloxymethoxy group is most preferred.

Where R3 represents an aralkyloxy group, the alkoxy part is an alkoxy group having from 1 to 4, preferably from 1 to 3, carbon atoms, such as those exemplified above in relation to R^1, especially the methoxy, ethoxy, propoxy or isopropoxy groups. The aryl part is as defined above and has from 6 to 10, preferably 6 or 10, ring carbon atoms. Examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups and such groups which are substituted by one or more of substituents D, defined above and examples of which have been given in relation to the same groups and atoms which may be represented by R^1. The alkoxy part may be substituted by one or more aryl groups, the maximum being dictated only by the number of substitutable positions and possibly also by steric constraints; however, from 1 to 3 aryl groups are normally preferred, 1 or 2 being more preferred and 1 being most preferred. Specific examples of the aralkyloxy groups include the benzyloxy, 1-naphthylmethoxy, 2-naphthylmethoxy, phenethyloxy, α-methylbenzyloxy, 3-phenylpropoxy, 2-phenylpropoxy, 1-phenylpropoxy, 4-phenylbutoxy, benzhydryloxy (i.e. diphenylmethoxy) and trityloxy (i.e. triphenylmethoxy) groups (of these, the benzyloxy and phenethyloxy groups are preferred), and such groups which are substituted by one or more of substituents D.

Where R^3 represents an alkanoyloxy group, this may be a straight or branched chain group and has from 1 to 18 carbon atoms. Examples of such groups include the formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, decanoyloxy, lauroyloxy, myristoyloxy, palmitoyloxy and stearoyloxy groups, of which those groups having from 1 to 12 carbon atoms are preferred, those having from 2 to 10 carbon atoms are more preferred, and those having from 2 to 5 carbon atoms are most preferred, especially the acetoxy, propionyloxy, butyryloxy, pivaloyloxy, nonanoyloxy and decanoyloxy groups, of which the acetoxy, propionyloxy, butyryloxy and pivaloyloxy groups are most preferred.

Where R^3 represents an alkenoyloxy group, this may be a straight or branched chain group and has from 3 to 6, more preferably 3 or 4, carbon atoms. Examples of such groups include the acryloyloxy, methacryloyloxy, 2-butenoyloxy, 2-pentenoyloxy and 2-hexenoyloxy groups, of which the acryloyloxy and methacryloyloxy groups are preferred.

Where R^3 represents a cycloalkylcarbonyloxy group, this has from 4 to 8, more preferably from 4 to 7, carbon atoms, that is the cycloalkyl group itself has from 3 to 7 ring carbon atoms. Examples of such groups include the cyclopropylcarbonyloxy, cyclobutylcarbonyloxy, cyclopentylcarbonyloxy, cyclohexylcabonyloxy and cycloheptylcarbonyloxy groups, of which the cyclopropylcarbonyloxy and cyclobutylcarbonyloxy groups are particularly preferred.

Where R^3 represents arylcarbonyloxy group, the aryl part is as defined above, and examples of such groups include the benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy, o-, m- and p-toluoyloxy, o-, m- and p-chlorobenzoyloxy, o-, m- and p-fluorobenzoyloxy, o-, m- and p-methoxybenzoyloxy, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dichlorobenzoyloxy, 2,4-difluorobenzoyloxy and 2,4,6-trifluorobenzoyloxy groups, preferably the benzoyloxy group.

Where R^3 represents an alkoxycarbonyloxy group, this may be a straight or branched chain alkoxycarbonyloxy group having from 2 to 5 carbon atoms, that is the alkoxy part has from 1 to 4 carbon atoms, and examples include the methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, sec-butoxycarbonyloxy and t-butoxycarbonyloxy groups. Of these, we prefer those alkoxycarbonyloxy groups having from 1 to 3 carbon atoms in the alkoxy part and the t-butoxycarbonyloxy group, more preferably the methoxycarbonyloxy, ethoxycarbonyloxy and t-butoxycarbonyloxy groups.

Where R^3 represents an aralkyloxycarbonyloxy group, the alkoxy part is an alkoxy group having from 1 to 4, preferably from 1 to 3, carbon atoms, such as those exemplified above in relation to R^1, especially the methoxy, ethoxy, propoxy or isopropoxy groups. The aryl part is as defined above and has from 6 to 10, preferably 6 or 10, ring carbon atoms. Examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups and such groups which are substituted by one or more of substituents D, defined above and examples of which have been given in relation to the same groups and atoms which may be represented by R^1. The alkoxy part may be substituted by one or more aryl groups, the maximum being dictated only by the number of substitutable positions and possibly also by steric constraints;

however, from 1 to 3 aryl groups are normally preferred, 1 or 2 being more preferred and 1 being most preferred. Specific examples of the aralkyloxycarbonyloxy groups include the benzyloxycarbonyloxy, 1-naphthylmethoxycarbonyloxy, 2-naphthylmethoxycarbonyloxy, phenethyloxycarbonyloxy, α-methylbenzyloxy. carbonyloxy, 3-phenylpropoxycarbonyloxy, 2-phenylpropoxycarbonyloxy, 1-phenylpropoxycarbonyloxy, 4-phenylbutoxycarbonyloxy, benzhydryloxycarbonyloxy and trityloxycarbonyloxy groups (of these, the benzyloxycarbonyloxy group is preferred), and such groups which are substituted by one or more of substituents D.

Where R^3 represents a group of formula $-NR^aR^b$, R^a and R^b are independently selected from the group consisting of hydrogen atoms, alkyl groups having from 1 to 4 carbon atoms and substituted alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one substituent selected from the group consisting of substituents C, defined above. Examples of the alkyl groups which may be represented by R^a and R^b are as given above in relation to R^1, and examples of the substituted alkyl groups which may be represented by R^a and R^b are the substituted alkyl groups corresponding to the substituted alkoxy groups, as given above in relation to R^3. Specific examples of these groups of formula $-NR^aR^b$ include amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutyamino, sec-butylamino, t-butylamino, dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, methylethylamino, methylpropylamino, N-(methoxymethyl)amino, N-(2-methoxyethyl)amino, N-(acetoxymethyl)amino, N-(pivaloyloxymethyl)amino, N-(benzoylmethyl)amino, N-(2-acetoxyethyl)amino, N-(2-pivaloyloxyethyl)amino and N-(2-benzoylethyl)amino groups, preferably the amino, methylamino, ethylamino, N-(acetoxymethyl)amino and N-(pivaloyloxymethyl)amino groups.

Where R^3 represents an aralkylamino group, the alkyl part is an alkyl group having from 1 to 4, preferably from 1 to 3, carbon atoms, such as those exemplified above in relation to R^1, especially the methyl, ethyl, propyl or isopropyl groups. The aryl part is as defined above and has from 6 to 10, preferably 6 or 10, ring carbon atoms. Examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups and such groups which are substituted by one or more of substituents D, defined above and examples of which have been given in relation to the same groups and atoms which may be represented by R^1. The alkyl part may be substituted by one or more aryl groups, the maximum being dictated only by the number of substitutable positions and possibly also by steric constraints; however, from 1 to 3 aryl groups are normally preferred, 1 or 2 being more preferred and 1 being most preferred. Specific examples of the aralkyl amino groups include the benzylamino, N-(1-naphthylmethyl)amino, N-(2-naphthylmethyl)amino, phenethylamino, N-(α-methylbenzyl)amino, N-(3-phenylpropyl)amino, N-(2-phenylpropyl)amino, N-(1-phenylpropyl)amino, N-(4-phenylbutyl)amino, benzhydrylamino and tritylamino groups (of these, the benzylamino group is preferred), and such groups which are substituted by one or more of substituents D.

Where R^3 represents an alkanoylamino group, this may be a straight or branched chain group and has from 1 to 18 carbon atoms. Examples of such groups include the formamido, acetamido, propionamido, butyramido, isobutyramido, valerylamino, isovalerylamino, pivaloylamino, hexanoylamino, heptanoylamino, octanoylamino, nonanoylamino, decanoylamino, lauroylamino, myristoylamino, palmitoylamino and stearoylamino groups, of which those groups having from 1 to 12 carbon atoms are preferred, those having from 2 to 10 carbon atoms are more preferred, and those having from 2 to 5 carbon atoms are most preferred, especially the acetamido, propionamido, butyramido, pivaloylamino, nonanoylamino and decanoylamino groups, of which the acetamido, propionamido, butyramido and pivaloylamino groups are most preferred.

Where R^3 represents an alkenoylamino group, this may be a straight or branched chain group and has from 3 to 6 carbon atoms. Examples of such groups include the acryloylamino, methacryloylamino, 2-butenoylamino, 2-pentenoylamino and 2-hexenoylamino groups, of which the acryloylamino and methacryloylamino groups are preferred.

Where R^3 represents a cycloalkylcarbonylamino group, this has from 4 to 8 carbon atoms, that is the cycloalkyl group itself has from 3 to 7 ring carbon atoms. Examples of such groups include the cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino and cycloheptylcarbonylamino groups, of which the cyclopropylcarbonylamino and cyclobutylcarbonylamino groups are particularly preferred.

Where R^3 represents arylcarbonylamino group, the aryl part is as defined above, and examples of such groups include the benzamido, 1-naphthoylamino, 2-naphthoylamino, o-, m- and p-toluoylamino, o-, m- and p-chlorobenzamido, o-, m- and p-fluorobenzamido, o-, m- and p-methoxybenzamido, 2,4-dichlorobenzamido, 2,4-difluorobenzamido and 2,4,6-trifluorobenzamido groups, preferably the benzamido group.

Where R^3 represents an alkoxycarbonylamino group, this may be a straight or branched chain alkoxycarbonylamino group having from 2 to 5 carbon atoms, that is the alkoxy part has from 1 to 4 carbon atoms, add examples include the methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, butoxycarbonylamino, isobutoxycarbonylamino, sec-butoxycarbonylamino and t-butoxycarbonylamino groups. Of these, we prefer those alkoxycarbonylamino groups having from 1 to 3 carbon atoms in the alkoxy part and the t-butoxycarbonylamino group, more preferably the methoxycarbonylamino, ethoxycarbonylamino and t-butoxycarbonylamino groups.

Where R^3 represents an aralkoxycarbonylamino group, the alkoxy part is an alkoxy group having from 1 to 4, preferably from 1 to 3, carbon atoms, such as those exemplified above in relation to R^1, especially the methoxy, ethoxy, propoxy or isopropoxy groups. The aryl part is as defined above and has from 6 to 10, preferably 6 or 10, ring carbon atoms. Examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups and such groups which are substituted by one or more of substituents D, defined above and examples of which have been given in relation to the same groups and atoms which may be represented by R^1. The alkoxy part may be substituted by one or more aryl groups, the maximum being dictated only by the number of substitutable positions and possibly also by steric constraints; however, from 1 to 3 aryl groups are normally pre-

ferred, 1 or 2 being more preferred and 1 being most preferred. Specific examples of the aralkyloxycarbonylamino groups include the benzyloxycarbonylamino, N-(1-naphthylmethoxycarbonyl)amino, N-(2-naphthylmethoxycarbonyl)amino, phenethyloxycarbonylamino, N-(α-methylbenzyloxycarbonyl-)amino, N-(3-phenylpropoxycarbonyl)amino, N-(2-phenylpropoxycarbonyl)amino, N-(1-phenylpropoxycarbonyl)amino, N-(4-phenylbutoxycarbonyl)amino, benzhydryloxycarbonylamino and trityloxycarbonylamino groups (of these, the benzyloxycarbonylamino group is preferred), and such groups which are substituted by one or more of substituents D.

Y represents a group of formula —NH— or an oxygen or sulfur atom, preferably an oxygen or sulfur atom, and more preferably a sulfur atom.

R^3 may be at either the 2- or the 3- position of the tetrahydropyrrolopyridyl, tetrahydrothienopyridyl or tetrahydrofuropyridyl group, but is preferably at the 2-position, especially when the Y is an oxygen or sulfur atom, i.e. on the tetrahydrothienopyridyl or tetrahydrofuropyridyl group.

In the compounds of the present invention, the carbon atom to which the group represented by R^2 is attached is an assymetric carbon atom, and other carbon atoms may be assymetric, and the compounds accordingly form optical isomers. Although these are all represented herein by a single molecular formula, the present invention includes both the individual, isolated isomers and mixtures, including racemates thereof. Where stereospecific synthesis techniques are employed or optically active compounds are employed as starting materials, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques.

In addition, when the compounds of the present invention have one or more carbon-carbon double bonds or one or more disubstituted cycloalkyl moieties, they form cis and trans isomers. The present invention includes both the individual, isolated isomers and mixtures thereof.

The compounds of the present invention can form acid addition salts. There is no particular restriction on the nature of these salts, provided that, where they are intended for therapeutic use, they are pharmaceutically acceptable. Where they are intended for non-therapeutic uses, e.g. as intermediates in the preparation of other, and possibly more active, compounds, even this restriction does not apply. Examples of such acid addition salts include: salts with mineral acids, especially hydrohalic acids (such as hydrofluoric acid, hydrobromic acid, hydroiodic acid or hydrochloric acid), nitric acid, carbonic acid, sulfuric acid or phosphoric acid; salts with lower alkylsulfonic acids, such as methanesulfonic acid, trifluoromethanesulfonic acid or ethanesulfonic acid; salts with arylsulfonic acids, such as benzenesulfonic acid or p-toluenesulfonic acid; and salts with organic carboxylic acids, such as acetic acid, propionic acid, butyric acid, fumaric acid, tartaric acid, oxalic acid, malonic acid, maleic acid, malic acid, succinic acid, benzoic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid or citric acid.

The compounds of the present invention may also readily form hydrates and these, also, form part of the present invention.

Additionally, when R^3 represents an amino group or a substituted amino group, the resulting compound can form a complex salt with a metal ion, and such complex salts also form part of the present invention. Examples of such complex salts include salts with calcium chloride, magnesium chloride, zinc chloride, ferric chloride, stannic chloride and nickel chloride.

Preferred classes of compounds of the present invention are those compounds of formulae (I) and tautomers and salts thereof in which:

(A) R^1 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group.

(B) R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a substituted benzoyl group having at least one fluorine substituent, or a 5,6-dihydro-1,4,2-dioxazin-3-yl group; and

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups.

(C) R^3 represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula —NR^aR^b

wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below;

and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

(D) Y represents an oxygen or sulfur atom.

Of these, we prefer those compounds in which R^1 is as defined in (A) above, R^2 is as defined in (B) above, R^3 is as defined in (C) above and Y is as defined in (D) above.

More preferred classes of compounds of the present invention are those compounds of formulae (I) and tautomers and salts thereof in which:

(E) R^1 represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group.

(F) R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom.

(G) R^3 represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, an amino group or a t-butoxycarbonylamino group.

Of these, we prefer those compounds in which R^1 is as defined in (E) above, R^2 is as defined in (F) above, R^3 is as defined in (G) above and Y is as defined in (D) above.

Still more preferred classes of compounds of the present invention are those compounds of formulae (I) and tautomers and salts thereof in which:

(H) R^1 represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group.

(I) R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group.

(J) Y represents a sulfur atom.

Of these, we prefer those compounds in which R^1 is as defined in (H) above, R^2 is as defined in (F) above, R^3 is as defined in (I) above and Y is as defined in (J) above.

The most preferred classes of compounds of the present invention are those compounds of formulae (I) and tautomers and salts thereof in which:

(K) R^1 represents a fluorine or chlorine atom.

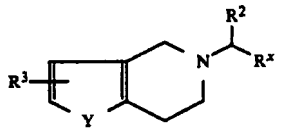
(L) R^2 represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom.

(M) R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms.

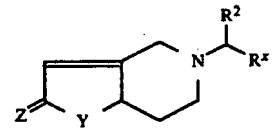
Of these, we prefer those compounds in which R^1 is as defined in (K) above, R^2 is as defined in (L) above, R^3 is as defined in (M) above and Y is as defined in (J) above.

In all of the above classes of compounds, we prefer that n should be from 1 to 3, especially 1 or 2, and most preferably 1.

Specific examples of preferred compounds of the present invention are those compounds of formula (II) or (IIa), in which R^x, R^2, R^3/Z and Y are as defined in the following Table 1. In the column headed "R^3/Z", the "R^3" applies to compounds of formula (II), whilst "Z" applies to compounds of formula (IIa):



(II)



(IIa)

In the Table, the following abbreviations are used to refer to certain substituent groups:

Ac	acetyl
Acr	acryloyl
tBoc	t-butoxycarbonyl
Boz	benzoyl
cBu	cyclobutyl
tBu	t-butyl
Bun	butenoyl
Byr	butyryl
iByr	isobutyryl
Bz	benzyl
Bzc	benzyloxycarbonyl
Car	carbamoyl
Dcn	decanoyl
Ddoz	5,6-dihydro-1,4,2-dioxazin-3-yl
Et	ethyl
Etc	ethoxycarbonyl
Fo	formyl
cHp	cycloheptyl
cHx	cyclohexyl
Hxn	hexanoyl
Lau	lauroyl
Me	methyl
Mec	methoxycarbonyl
Mod	(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl
Nnn	nonanoyl
Plt	palmitoyl
Ph	phenyl
Phth	phthalidyl
Piv	pivaloyl
cPn	cyclopentyl
cPr	cyclopropyl
Prn	propionyl
Va	valeryl
iVa	isovaleryl

TABLE 1

Cpd. No.	Formula	R^x	R^2	R^3/Z	Y
1	(II)	Ph	Ddoz	H	S
2	(II)	2-FPh	Ddoz	H	S
3	(II)	2-ClPh	Ddoz	H	S
4	(II)	2-CNPh	Ddoz	H	S
5	(II)	2-NO_2Ph	Ddoz	H	S
6	(II)	2-CHF_2Ph	Ddoz	H	S
7	(II)	2,6-diFPh	Ddoz	H	S
8	(II)	2-F, 6-ClPh	Ddoz	H	S
9	(II)	2-FPh	Ac	H	S
10	(II)	2-ClPh	Ac	H	S
11	(II)	2-CNPh	Ac	H	S
12	(II)	2-NO_2Ph	Ac	H	S
13	(II)	2-CF_3Ph	Ac	H	S
14	(II)	2,6-diFPh	Ac	H	S
15	(II)	2-F, 6-ClPh	Ac	H	S
16	(II)	2,4-diFPh	Ac	H	S
17	(II)	2-F, 6-CNPh	Ac	H	S
18	(II)	Ph	Prn	H	S
19	(II)	2-FPh	Prn	H	S
20	(II)	2-ClPh	Prn	H	S
21	(II)	2-BrPh	Prn	H	S
22	(II)	2-IPh	Prn	H	S
23	(II)	2-HOPh	Prn	H	S
24	(II)	2-NO_2Ph	Prn	H	S
25	(II)	2-Cl, 5-NH_2Ph	Prn	H	S
26	(II)	2-CNPh	Prn	H	S
27	(II)	2-F, 5-HOOCPh	Prn	H	S
28	(II)	2-F, 4-MePh	Prn	H	S
29	(II)	2-CF_3Ph	Prn	H	S
30	(II)	2-F, 4-MeOPh	Prn	H	S
31	(II)	2-CHF_2OPh	Prn	H	S
32	(II)	2-CF_3OPh	Prn	H	S
33	(II)	3-CH_2FOPh	Prn	H	S
34	(II)	4-MeSPh	Prn	H	S
35	(II)	2-CHF_2SPh	Prn	H	S
36	(II)	3-CF_3SPh	Prn	H	S

TABLE 1-continued

Cpd. No.	Formula	R^x	R^2	R^3/Z	Y
37	(II)	2-$MeSO_2$Ph	Prn	H	S
38	(II)	2-$EtSO_2$Ph	Prn	H	S
39	(II)	2-CF_3SO_2Ph	Prn	H	S
40	(II)	4-CarPh	Prn	H	S
41	(II)	3-NH_2SO_2Ph	Prn	H	S
42	(II)	2-FoPh	Prn	H	S
43	(II)	2-AcPh	Prn	H	S
44	(II)	2-CF_3COPh	Prn	H	S
45	(II)	2,6-diFPh	Prn	H	S
46	(II)	2-F, 6-ClPh	Prn	H	S
47	(II)	2,4,6-triFPh	Prn	H	S
48	(II)	2,3,4,5,6-pentaFPh	Prn	H	S
49	(II)	2-F, 6-CNPh	Prn	H	S
50	(II)	2-F, 6-NO_2Ph	Prn	H	S
51	(II)	2,6-diF, 4-MePh	Prn	H	S
52	(II)	2,4-diClPh	Prn	H	S
53	(II)	2-F, 4-HOPh	Prn	H	S
54	(II)	2-Cl, 4-MecPh	Prn	H	S
55	(II)	2-F, 6-CHF_2OPh	Prn	H	S
56	(II)	2-Cl, 4-EtPh	Prn	H	S
57	(II)	2-F, 5-EtOPh	Prn	H	S
58	(II)	Ph	cPrCO	H	S
59	(II)	2-FPh	cPrCO	H	S
60	(II)	2-ClPh	cPrCO	H	S
61	(II)	2-BrPh	cPrCO	H	S
62	(II)	2-IPh	cPrCO	H	S
63	(II)	2-HOPh	cPrCO	H	S
64	(II)	2-NO_2Ph	cPrCO	H	S
65	(II)	2-Cl, 5-NH_2Ph	cPrCO	H	S
66	(II)	2-CNPh	cPrCO	H	S
67	(II)	2-F, 5-HOOCPh	cPrCO	H	S
68	(II)	2-F, 4-MePh	cPrCO	H	S
69	(II)	2-CF_3Ph	cPrCO	H	S
70	(II)	2-F, 4-MeOPh	cPrCO	H	S
71	(II)	2-CHF_2OPh	cPrCO	H	S
72	(II)	2-CF_3OPh	cPrCO	H	S
73	(II)	3-CH_2FOPh	cPrCO	H	S
74	(II)	4-MeSPh	cPrCO	H	S
75	(II)	2-CHF_2SPh	cPrCO	H	S
76	(II)	3-CF_3SPh	cPrCO	H	S
77	(II)	2-$MeSO_2$Ph	cPrCO	H	S
78	(II)	2-$EtSO_2$Ph	cPrCO	H	S
79	(II)	2-CF_3SO_2Ph	cPrCO	H	S
80	(II)	4-CarPh	cPrCO	H	S
81	(II)	3-NH_2SO_2Ph	cPrCO	H	S
82	(II)	2-FoPh	cPrCO	H	S
83	(II)	2-AcPh	cPrCO	H	S
84	(II)	2-CF_3COPh	cPrCO	H	S
85	(II)	2,6-diFPh	cPrCO	H	S
86	(II)	2-F, 6-ClPh	cPrCO	H	S
87	(II)	2,4,6-triFPh	cPrCO	H	S
88	(II)	2,3,4,5,6-pentaFPh	cPrCO	H	S
89	(II)	2-F, 6-CNPh	cPrCO	H	S
90	(II)	2-F, 6-NO_2Ph	cPrCO	H	S
91	(II)	2,6-diF, 4-MePh	cPrCO	H	S
92	(II)	2,4-diClPh	cPrCO	H	S
93	(II)	2-F, 4-HOPh	cPrCO	H	S
94	(II)	2-Cl, 4-EtcPh	cPrCO	H	S
95	(II)	2-F, 6-CHF_2OPh	cPrCO	H	S
96	(II)	2-Cl, 4-EtPh	cPrCO	H	S
97	(II)	2-F, 5-EtOPh	cPrCO	H	S
98	(II)	2-FPh	3-FPrn	H	S
99	(II)	2-ClPh	3-FPrn	H	S
100	(II)	2-CNPh	3-FPrn	H	S
101	(II)	2,6-diFPh	3-FPrn	H	S
102	(II)	2-F, 6-ClPh	3-FPrn	H	S
103	(II)	2-F, 6-CNPh	3-FPrn	H	S
104	(II)	2-NO_2Ph	3-FPrn	H	S
105	(II)	2-F, 4-CNPh	3-FPrn	H	S
106	(II)	2-FPh	cBuCO	H	S

TABLE 1-continued

Cpd. No.	Formula	R^x	R^2	R^3/Z	Y
107	(II)	2-ClPh	cBuCO	H	S
108	(II)	2-CNPh	cBuCO	H	S
109	(II)	2-FPh	$HOCH_2CO$	H	S
110	(II)	2-ClPh	$HOCH_2CO$	H	S
111	(II)	2-CNPh	CF_3CO	H	S
112	(II)	2-FPh	CF_3CO	H	S
113	(II)	2-ClPh	CF_3CO	H	S
114	(II)	2-FPh	Fo	H	S
115	(II)	2-ClPh	Fo	H	S
116	(II)	2-FPh	Byr	H	S
117	(II)	2-ClPh	Byr	H	S
118	(II)	2-FPh	iByr	H	S
119	(II)	2-ClPh	iByr	H	S
120	(II)	2-FPh	Va	H	S
121	(II)	2-ClPh	Va	H	S
122	(II)	2-FPh	Piv	H	S
123	(II)	2-F, 6-ClPh	Piv	H	S
124	(II)	2-FPh	iVa	H	S
125	(II)	2-ClPh	Hxn	H	S
126	(II)	2-FPh	Dcn	H	S
127	(II)	2-ClPh	1-Bun	H	S
128	(II)	2-FPh	cPnCO	H	S
129	(II)	2-FPh	cHxCO	H	S
130	(II)	2-FPh	cHpCO	H	S
131	(II)	2-FPh	CH_2FCO	H	S
132	(II)	2-FPh	CHF_2CO	H	S
133	(II)	2-ClPh	CHF_2CO	H	S
134	(II)	2-CNPh	CHF_2CO	H	S
135	(II)	2-FPh	$MeO—CH_2CO$	H	S
136	(II)	2-ClPh	$MeO—CH_2CO$	H	S
137	(II)	2-FPh	$NC—CH_2CO$	H	S
138	(II)	2-ClPh	$NC—CH_2CO$	H	S
139	(II)	2,6-diFPh	$NC—CH_2CO$	H	S
140	(II)	2-FPh	3-ClPrn	H	S
141	(II)	2-ClPh	3-ClPrn	H	S
142	(II)	2-FPh	3-HOPrn	H	S
143	(II)	2-ClPh	3-HOPrn	H	S
144	(II)	2-FPh	3-MeOPrn	H	S
145	(II)	2-FPh	3-CNPrn	H	S
146	(II)	2-FPh	4-FByr	H	S
147	(II)	2-ClPh	4-ClByr	H	S
148	(II)	2-FPh	4-FBoz	H	S
149	(II)	2-ClPh	4-FBoz	H	S
150	(II)	2-CNPh	4-FBoz	H	S
151	(II)	2-FPh	2,4-diFBoz	H	S
152	(II)	2-ClPh	2,4-diFBoz	H	S
153	(II)	$2-NO_2Ph$	2,4-diFBoz	H	S
154	(II)	2-FPh	3-BrPrn	H	S
155	(II)	2-FPh	3-IPrn	H	S
156	(II)	2-FPh	Ac	H	O
157	(II)	2-ClPh	Ac	H	O
158	(II)	2-CNPh	Ac	H	O
159	(II)	$2-NO_2Ph$	Ac	H	O
160	(II)	2-FPh	Prn	H	O
161	(II)	2-ClPh	Prn	H	O
162	(II)	2-CNPh	Prn	H	O
163	(II)	$2-NO_2Ph$	Prn	H	O
164	(II)	2-FPh	3-FPrn	H	O
165	(II)	2-ClPh	3-FPrn	H	O
166	(II)	2-CNPh	3-FPrn	H	O
167	(II)	$2-NO_2Ph$	3-FPrn	H	O
168	(II)	2-FPh	cPrCO	H	O
169	(II)	2-ClPh	cPrCO	H	O
170	(II)	2-CNPh	cPrCO	H	O
171	(II)	$2-NO_2Ph$	cPrCO	H	O
172	(II)	2,6-diFPh	cPrCO	H	O
173	(II)	2-F, 6-ClPh	cPrCO	H	O
174	(II)	2,6-diFPh	4-FBoz	H	S
175	(II)	2-FPh	cPrCO	$2-NO_2$	S
176	(II)	2-FPh	cPrCO	$2-NH_2$	O
177	(II)	2-FPh	cPrCO	$2-NH_2$	S
178	(II)	2-FPh	cPrCO	2-AcNH	O
179	(II)	2-FPh	cPrCO	2-AcNH	S
180	(II)	2-FPh	cPrCO	2-ByrNH	O
181	(II)	2-FPh	cPrCO	2-ByrNH	S
182	(II)	2-FPh	cPrCO	2-PivNH	S
183	(II)	2-FPh	cPrCO	2-tBocNH	O
184	(II)	2-FPh	cPrCO	2-tBocNH	S
185	(II)	2-FPh	cPrCO	2-HO	O
186	(II)	2-ClPh	cPrCO	2-HO	S

TABLE 1-continued

Cpd. No.	Formula	R^x	R^2	R^3/Z	Y
187	(II)	2-FPh	Prn	2-HO	S
188	(II)	2-FPh	cPrCO	2-HO	S
189	(II)	2-FPh	cPrCO	2-AcO	O
190	(II)	2-FPh	cPrCO	2-AcO	S
191	(II)	2-FPh	cPrCO	2-PrnO	O
192	(II)	2-FPh	cPrCO	2-PrnO	S
193	(II)	2-FPh	cPrCO	2-ByrO	O
194	(II)	2-FPh	cPrCO	2-ByrO	S
195	(II)	2-FPh	cPrCO	2-PivO	O
196	(II)	2-FPh	cPrCO	2-PivO	S
197	(II)	2-FPh	cPrCO	2-VaO	S
198	(II)	2-FPh	cPrCO	2-HxnO	S
199	(II)	2-FPh	cPrCO	2-NnnO	S
200	(II)	2-FPh	cPrCO	2-DcnO	S
201	(II)	2-FPh	cPrCO	2-PhtO	S
202	(II)	2-FPh	cPrCO	2-BozO	S
203	(II)	2-FPh	cPrCO	2-tBocO	S
204	(II)	2-FPh	cPrCO	2-tBuO	S
205	(II)	2-FPh	cPrCO	2-BzO	S
206	(II)	2-FPh	cPrCO	$2-MeOCH_2O$	S
207	(II)	2-FPh	cPrCO	$2-PivOCH_2O$	S
208	(II)	2-FPh	cPrCO	2-PhthO	S
209	(II)	2-FPh	cPrCO	2-ModO	S
210	(II)	2-FPh	cPrCO	2-MeO	S
211	(II)	2-FPh	cPrCO	2-EtO	S
212	(II)	2-FPh	cPrCO	2-LauO	S
213	(II)	2-FPh	cPrCO	2-AcrO	S
214	(II)	2-FPh	cPrCO	2-cHxCOO	S
215	(II)	2-FPh	cPrCO	2-MecO	S
216	(II)	2-FPh	cPrCO	2-EtcO	S
217	(II)	2-FPh	cPrCO	2-FoNH	S
218	(II)	2-FPh	cPrCO	2-PrnNH	S
219	(II)	2-FPh	cPrCO	2-MeNH	S
220	(II)	2-FPh	cPrCO	2-EtNH	S
221	(II)	2-FPh	cPrCO	$2-NMe_2$	S
222	(II)	2-FPh	cPrCO	2-AcrNH	S
223	(II)	2-FPh	cPrCO	2-cHxCONH	S
224	(II)	2-FPh	cPrCO	2-MecNH	S
225	(II)	2-FPh	cPrCO	2-EtcNH	S
226	(II)	2-FPh	cPrCO	2-BozNH	S
227	(II)	2-FPh	cPrCO	2-BozO	O
228	(II)	2-FPh	cPrCO	2-tBocO	O
229	(II)	2-FPh	Prn	$2-NO_2$	S
230	(II)	2-FPh	cPrCO	2-BzcO	S
231	(II)	2-FPh	cPrCO	2-BzcNH	S
232	(IIa)	2-FPh	cPrCO	O	O
233	(IIa)	2-ClPh	cPrCO	O	S
234	(IIa)	2-FPh	Prn	O	S
235	(IIa)	2-FPh	cPrCO	O	S
236	(II)	2-FPh	Prn	2-AcO	S
237	(II)	2-FPh	Prn	2-PrnO	S
238	(II)	2-FPh	Prn	2-ByrO	S
239	(II)	2-FPh	Prn	2-PivO	S
240	(II)	2-FPh	Prn	2-VaO	S
241	(II)	2-FPh	Prn	2-HxnO	S
242	(II)	2-FPh	Prn	2-MecO	S
243	(II)	2-FPh	Prn	2-EtcO	S
244	(II)	2-FPh	Prn	2-tBocO	S
245	(II)	2-FPh	Prn	2-BozO	S
246	(II)	2-FPh	Prn	$2-NH_2$	S
247	(II)	2-FPh	Prn	2-AcNH	S
248	(II)	2-FPh	Prn	2-PrnNH	S
249	(II)	2-FPh	Prn	2-ByrNH	S
250	(II)	2-FPh	Prn	2-tBocNH	S
251	(II)	2-FPh	Prn	2-BzcNH	S
252	(II)	2-ClPh	cPrCO	2-AcO	S
253	(II)	2-ClPh	cPrCO	2-PrnO	S
254	(II)	2-ClPh	cPrCO	2-ByrO	S
255	(II)	2-ClPh	cPrCO	2-PivO	S
256	(II)	2-ClPh	cPrCO	2-VaO	S
257	(II)	2-ClPh	cPrCO	2-HxnO	S
258	(II)	2-ClPh	cPrCO	2-MecO	S
259	(II)	2-ClPh	cPrCO	2-EtcO	S
260	(II)	2-ClPh	cPrCO	2-tBocO	S
261	(II)	2-ClPh	cPrCO	2-BozO	S
262	(II)	2-ClPh	cPrCO	$2-NH_2$	S
263	(II)	2-ClPh	cPrCO	2-AcNH	S
264	(II)	2-ClPh	cPrCO	2-PrnNH	S
265	(II)	2-ClPh	cPrCO	2-ByrNH	S
266	(II)	2-ClPh	cPrCO	2-tBocNH	S

TABLE 1-continued

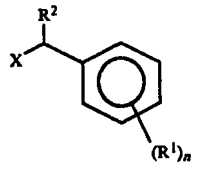
Cpd. No.	Formula	R^x	R^2	R^3/Z	Y
267	(II)	2-ClPh	cPrCO	2-BzcNH	S
268	(II)	2-FPh	cPrCO	2-$MeOCH_2NH$	S
269	(II)	2-FPh	cPrCO	2-PhthNH	S
270	(II)	2-FPh	cPrCO	2-ModNH	S
271	(II)	2-FPh	cPrCO	2-$PivOCH_2NH$	S
272	(II)	2-FPh	2-FcPrCO	H	S
273	(II)	2-FPh	2-FcPrCO	H	O
274	(II)	2-FPh	2-FcPrCO	2-OH	S
275	(IIa)	2-FPh	2-FcPrCO	O	S
276	(II)	2-FPh	2-FcPrCO	2-AcO	S
277	(II)	2-FPh	2-FcPrCO	2-ByrO	S
278	(II)	2-FPh	2-FcPrCO	2-PivO	S
279	(II)	2-FPh	2-FcPrCO	2-$PivOCH_2O$	S
280	(II)	2-ClPh	2-FcPrCO	H	S
281	(II)	2-ClPh	2-FcPrCO	2-OH	S
282	(IIa)	2-ClPh	2-FcPrCO	O	S
283	(II)	2-ClPh	2-FcPrCO	2-AcO	S
284	(II)	2-ClPh	2-FcPrCO	2-ByrO	S
285	(II)	2-ClPh	2-FcPrCO	2-PivO	S
286	(II)	2-ClPh	2-FcPrCO	2-$PivOCH_2O$	S
287	(II)	2-FPh	2,2-diFcPrCO	H	S
288	(II)	2-FPh	2,2-diFcPrCO	2-OH	S
289	(IIa)	2-FPh	2,2-diFcPrCO	O	S
290	(II)	2-FPh	2,2-diFcPrCO	2-AcO	S
291	(II)	2-FPh	2,2-diFcPrCO	2-ByrO	S

Of the compounds listed above, the following are preferred, that is to say Compounds No. 2, 3, 7, 9, 10, 11, 12, 19, 20, 24, 26, 29, 58. 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 89, 90, 98, 99, 106, 107, 108, 109, 111, 112, 113, 114, 116, 117, 118, 119, 120, 121, 122, 124, 125, 128, 129, 131, 132, 133, 135, 137, 140, 142, 144, 149, 151, 156, 160, 168, 177, 184, 186, 187, 188, 190, 192, 194, 196, 197, 198, 199, 200, 201, 203, 204, 206, 207, 208, 209, 210, 233, 234, 235, 236, 238, 239, 252, 253, 254, 255, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289 and 290, of which Compounds No. 9, 10, 19, 20, 59, 60, 63, 64, 66, 69, 71, 72, 75, 76, 83, 84, 85, 86, 98, 106, 113, 116, 118, 120, 122, 125, 128, 129, 131, 132, 186, 187, 188, 190, 192, 194, 196, 197, 198, 199, 200, 203, 207, 209, 233, 234, 235, 236, 238, 239, 252, 253, 254, 255, 274, 275, 276, 277, 278, 279, 281, 282, 283, 284, 285 and 286 are more preferred.

The most preferred compounds are Compounds No.:

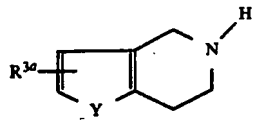
19. 5-(2-Fluoro-α-propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
59. 5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
60. 5-(2-Chloro-60 -cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
190. 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
192. 5-(-60 Cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
194. 2-Butyryloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
196. 5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
197. 5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-valeryloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
198. 5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-hexanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
203. 2-t-Butoxycarbonyloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
207. 5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
233. 5-(2-Chloro-α-cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;
234. 5-(2-Fluoro-α-propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;
235. 5 (α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;
252. 2-Acetoxy-5-(2-chloro-α-cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
275. 5[α-(2-Fluorocyclopropylcarbonyl-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;
276. 2-Acetoxy-5-[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

The compounds of the present invention can be prepared by a variety of methods, whose general techniques are known in the art for the preparation of compounds of this type. For example, they may be prepared by reacting a compound of formula (III):



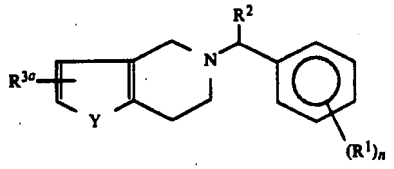
(III)

(in which R^1, R^2 and n are as defined above and X represents a halogen atom, for example a fluorine, chlorine, bromine or iodine atom, preferably a chlorine or bromine atom) with a compound of formula (IV):



(IV)

(in which Y is as defined above and R^{3a} represents a hydrogen atom or a hydroxy or nitro group) to give a compound of formula (Ic):



(Ic)

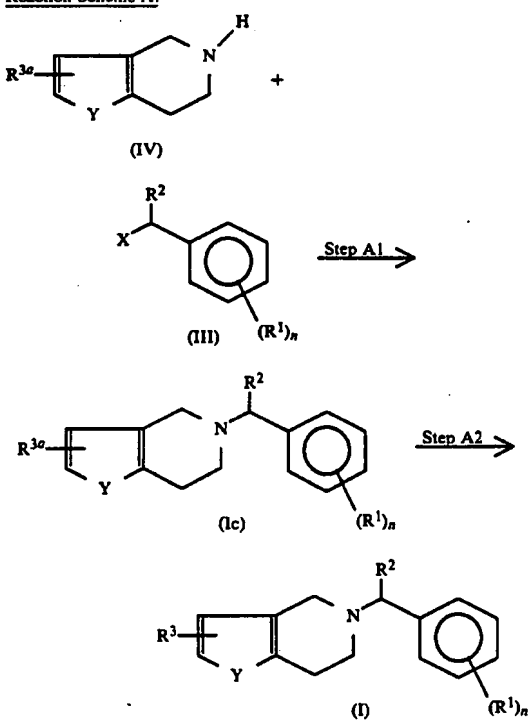
(in which R^1, R^2, R^{3a}, n and Y are as defined above).

If required, this compound of formula (Ic) may then be subjected to one or more appropriate reactions, as explained in more detail hereafter, to convert the hy-

droxy or nitro group represented by R^{3a} to any other group represented by R^3, as defined above.

These reactions may be summarized in the following Reaction Scheme A:

Reaction Scheme A:



In the above formulae, R^1, R^2, R^3, R^{3a}, X, Y and n are as defined above.

In Step A1 of this Reaction Scheme, the substituted benzyl halide of formula (III) is reacted with a condensed hydropyridyl compound of formula (IV), to give the compound of formula (Ic). This reaction may be carried out in the presence or absence of an inert solvent (preferably in the presence of an inert solvent) and in the presence or absence of a base (preferably in the presence of a base).

There is no specific limitation on the nature of the base employed, and any base known for use in reactions of this type may equally be used here. Examples of suitable bases include: organic amines, such as triethylamine, tributylamine, N-methylmorpholine, pyridine, 4-dimethylaminopyridine, picoline, lutidine, collidine, 1,8-diazabicyclo[5.4.0]undec-7-ene or 1,5-diazabicyclo[4.3.0]non-5-ene; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide or potassium t-butoxide; alkali metal carbonates, such as sodium carbonate or potassium carbonate; and alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide. Of these, the alkali metal carbonates are preferred. The amount of base employed is not critical, but we would generally recommend an amount of base of from an equimolar amount to 5 times the equimolar amount with respect to the starting material of formula (III). Where an excess of the starting material of formula (IV) is employed, this may also function as the base. Also, if an excess of an organic amine is employed as the base, this may additionally serve as the solvent.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; ketones, such as acetone or methyl ethyl ketone; esters, such as ethyl acetate; alcohols, such as methanol, ethanol, propanol, isopropanol or butanol; nitriles, such as acetonitrile; amides, such as N,N-dimethylformamide, N,N-dimethyl acetamide, N-methyl-2-pyrrolidone or hexamethyl phosphoric triamide; and sulfoxides, such as dimethyl sulfoxide. Of these, the amides or the sulfoxides are preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 200° C. (more preferably at from about room temperature to 150° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

After completion of the reaction, the desired compound of formula (Ic) can be obtained from the reaction mixture by conventional means. For example, if the compound is produced immediately in the form of crystals, these can be separated simply by filtration. Alternatively, a suitable recovery procedure comprises: adding water; neutralizing the mixture, if necessary; extracting the mixture with a water-immiscible organic solvent; drying the extract; and distilling the solvent off. If necessary, the product thus obtained can be further purified by conventional means, such as recrystallization or the various chromatography techniques, for example preparative thin layer chromatography or column chromatography, notably column chromatography.

In the optional second step of this reaction, Step A2, the resulting compound of formula (Ic) is converted, if desired, to a compound of formula (I). This reaction may involve any one or more of the following reactions:

(1) Where R^{3a} represents a hydroxy group, alkylation, aralkylation or acylation of this hydroxy group;

(2) Where R^{3a} represents a nitro group, conversion of this nitro group to an amino group;

(3) Alkylation, aralkylation or acylation of the amino group obtained as described in (2) above.

Alkylation, aralkylation or acylation of the hydroxy group in Step A2(1) is carried out in an inert solvent and in the presence of a base by reacting a hydroxy compound of formula (Ic) (R^{3a} represents a hydroxy group) with a corresponding alkylating, aralkylating or acylating agent, for example an alkyl halide, aralkyl halide, acyl halide or acid anhydride. The nature of this compound will, of course, depend on the nature of the group which it is desired to introduce into the compound of formula (I). However, examples of suitable compounds are as follows:

alkyl halides having from 1 to 4 carbon atoms, such as methyl iodide, ethyl bromide, ethyl iodide, propyl chloride, propyl bromide, butyl chloride or butyl iodide;

aralkyl halides having from 7 to 14 carbon atoms, such as benzyl chloride, benzyl bromide, p-methylbenzyl chloride, p-methoxybenzyl chloride, p-chlorobenzyl chloride, p-fluorobenzyl chloride or naphthylmethyl chloride;

alkyl halides from 1 to 4 carbon atoms which are substituted by an alkoxy group having from 1 to 4 carbon atoms, by an alkanoyloxy group having from 1 to 6 carbon atoms or by an arylcarbonyloxy group having from 7 to 11 carbon atoms, such as methoxy methyl chloride, 1-methoxyethyl chloride, 2-methoxyethyl chloride, 1-methoxypropyl chloride, 1-methoxybutyl chloride, ethoxymethyl chloride, propoxymethyl chloride, butoxymethyl chloride, acetoxymethyl chloride, 1-acetoxyethyl chloride, 2-acetoxyethyl chloride, 1-acetoxypropyl chloride, 1-acetoxybutyl chloride, propionyloxymethyl chloride, butyryloxymethyl chloride, valeryloxymethyl chloride, pivaloyloxymethyl chloride, benzoyloxymethyl cchloride, 1-benzoyloxyethyl chloride, p-methylbenzoyloxymethyl chloride, p-methoxybenzoyloxymethyl chloride, p-chlorobenzoyloxymethyl chloride, p-fluorobenzoyloxymethyl chloride or naphthoyloxymethyl chloride;

alkanoyl halides having from 2 to 18 carbon atoms or a mixed acid anhydride of one such corresponding acid with formic acid, such as acetyl chloride, propionyl chloride, butyryl chloride, butyryl bromide, valeryl chloride, isovaleryl chloride, pivaloyl chloride, hexanoyl chloride, nonanoyl chloride, decanoyl chloride, lauroyl chloride, palmitoyl chloride, stearoyl chloride, mixed acid anhydride of formic acid and acetic acid, acetic anhydride, propionic anhydride or butyric anhydride;

alkenoyl chlorides having from 3 to 6 carbon atoms, such as acryloyl chloride, methacryloyl chloride, crotonoyl chloride or 2-hexenoyl chloride;

cycloalkanecarbonyl halides having from 3 to 7 carbon atoms in the cycloalkane part, such as cyclopropanecarbonyl chloride, cyclobutanecarbonyl chloride, cyclopentanecarbonyl chloride, cyclohexanecarbonyl chloride or cycloheptanecarbonyl chloride;

arylcarbonyl halides having from 6 to 10 carbon atoms in the aryl part, such as benzoyl chloride, p-methylbenzoyl chloride, p-methoxybenzoyl chloride, p-chlorobenzoyl chloride, p-fluorobenzoyl chloride or naphthoyl chloride;

alkoxycarbonyl halides having from 1 to 4 carbon atoms in the alkoxy part, or an alkyl carbonate anhydride having from 1 to 4 carbon atoms in the alkyl part, such as methoxycarbonyl chloride, ethoxycarbonyl chloride, propoxycarbonyl chloride, isopropoxycarbonyl chloride, butoxycarbonyl chloride, t-butoxycarbonyl chloride, dimethyl dicarbonate, diethyl dicarbonate, dipropyl dicarbonate, diisopropyl dicarbonate, dibutyl dicarbonate or di-t-butyl dicarbonate;

aralkyloxycarbonyl halides having from 7 to 14 carbon atoms in the aralkyl part, such as benzyl oxycarbonyl chloride, p-methylbenzyloxycarbonyl chloride, p-methoxybenzyloxycarbonyl chloride, p-chlorobenzyloxycarbonyl chloride, p-fluorobenzyloxycarbonyl chloride or naphthylmethoxycarbonyl chloride;

phthalidyl halides, such as phthalidyl chloride; or substituted methyl halides, such as (5-methyl- or 5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl chloride.

The base employed is not critical to the invention, provided that it has no adverse effect on other parts of the molecule, and any base commonly used in reactions of this type may equally be used here. Examples of suitable bases include: alkali metal hydrides, such as lithium hydride or sodium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide or potassium t-butoxide; alkali metal carbonates, such as sodium carbonate or potassium carbonate; and alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide. Of these, the alkali metal hydrides are preferred.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; ketones, such as acetone or methyl ethyl ketone; esters, such as ethyl acetate; nitriles, such as acetonitrile; amides, such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone or hexamethylphosphoric triamide; and sulfoxides, such as dimethyl sulfoxide. Of these, the amides are preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from −10° C. to 100° C. (more preferably from 0° C. to 50° C.), although this may vary, depending on the nature of the compound of formula (Ic) and the solvent. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice.

The reaction of Step A2(2), which comprises the conversion of the nitro group represented by R^{3a} in the compound of formula (Ic) into an amino group is preferably effected, in an inert solvent and in the presence of an acid, by reaction of a nitro compound of formula (Ic) in which R^{3a} represents a nitro group with a reducing agent, for example a metal powder. Suitable reducing metal powders include powders of iron, tin or zinc. Of these, iron or tin powder is preferred.

Suitable acids include: mineral acids, such as hydrochloric acid or sulfuric acid; and organic acids, such as acetic acid, trifluoroacetic acid, methanesulfonic acid or p-toluensulfonic acid. Of these, hydrochloric acid or acetic acid is preferred.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: water; ethers, such as diethyl ether, tetrahydrofuran or dioxane; alcohols, such as methanol or ethanol; the acid employed for the reaction, as mentioned above; or a mixture of any two or more of these

solvents. Of these, we prefer to use a mixture of water with an acid.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from −10° C. to 100° C. (more preferably from 0° C. to 50° C.), although this may vary depending on the nature of the starting material of formula (Ic) and on the solvent employed. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 15 minutes to 20 hours (more preferably from 30 minutes to 10 hours) will usually suffice. If this reaction is carried out in an organic acid and in the presence of one of the acid anhydrides mentioned later in connection with the reaction of Step A2(3), this reaction affords an amino-acylated compound.

Conversion of the nitro group into an amino group can be also conducted in a similar manner to Step C2(4) of Reaction Scheme C as described hereafter, and, in this case, any nitro group contained in R^1 is converted into an amino group at the same time.

Alkylation, aralkylation or acylation of the amino group can be conducted by reacting an amino compound of formula (Ic) in which R^3 represents an amino group with a corresponding alkyl halide, aralkyl halide, acyl halide or acid anhydride [for example: an alkyl halide having from 1 to 4 carbon atoms; an alkyl halide having from 1 to 4 carbon atoms which is substituted by an alkoxy group having from 1 to 4 carbon atoms, by an alkanoyloxy group having from 1 to 6 carbon atoms or by an arylcarbonyloxy group having from 6 to 10 carbon atoms in the aryl moiety; an aralkyl halide having from 7 to 14 carbon atoms; an alkanoyl halide having from 2 to 18 carbon atoms or a mixed acid anhydride of a corresponding acid with formic acid; an alkenoyl halide having from 3 to 6 carbon atoms; a cycloalkanecarbonyl halide having from 3 to 7 carbon atoms in the cycloalkane moiety; an arylcarbonyl halide having from 6 to 10 carbon atoms in the aryl moiety; an alkoxycarbonyl halide having from 1 to 4 carbon atoms in the alkoxy moiety; an alkyl carbonate anhydride having from 1 to 4 carbon atoms in the alkyl moiety; an aralkyloxycarbonyl halide having from 7 to 14 carbon atoms in the aralkyl moiety; a phthalidyl halide; or a (5-methyl or 5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl halide, all as exemplified above in relation to Step A2(1)]. This reaction normally and preferably takes place in an inert solvent and in the presence of a base. If it is desired to prepare a mono-alkylamino compound having from 1 to 4 carbon atoms, we prefer to use about an equimolar amount of an alkyl halide having from 1 to 4 carbon atoms with respect to the compound of formula (I); on the other hand, the desired compound is a di-alkylamino compound having from 1 to 4 carbon atoms in each alkyl moiety, it is preferred to use more than about 2 moles of an alkyl halide having from 1 to 4 carbon atoms per mole of the compound of formula (I).

The reaction is essentially the same as that employed in Step A1, and may be carried out using the the reaction conditions, base and solvent as described above in relation to that reaction.

After completion of the reaction or any of the reactions described above, the desired compound can be obtained from the reaction mixture by conventional means. For example, one suitable recovery procedure comprises: filtering off any insoluble matter; adding water to the filtrate; if necessary, neutralizing the resulting mixture; extracting it with a water-immiscible organic solvent, such as ethyl acetate; drying it; and distilling off the solvent. If necessary, the product thus obtained can be further purified by conventional means, such as recrystallization or the various chromatography techniques, for example preparative thin layer chromatography or column chromatography, notably column chromatography.

A salt of the compound of formula (I) can be prepared by conventional means, as is well known in the art. For example, the compound of formula (I) is treated with an acid, such as hydrochloric acid or maleic acid, in an inert solvent, such as diethyl ether or diisopropyl ether, and the separated crystals are recovered by filtration.

An optically active compound of formula (I) can be prepared by using a corresponding optically active benzyl halide of formula (II) as the starting material, or by optical resolution of a racemic compound of formula (I) by conventional means, such as fractional crystallization or liquid chromatography.

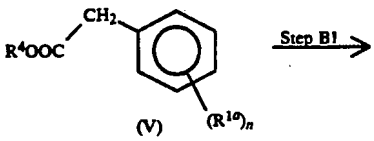
The condensed hydropyridyl compound of formula (IV), used as one of the starting materials, is known or may easily be prepared by any known method [for example, M. Podesta et al., Eur. J. Med. Chem. - Chim. Ther. 9 (5), 487–490 (1974); and Japanese Patent Kokai Application No. Sho 61-246186]. Compounds of formula (IV) having a nitro group as the group R^{3a} are known or can be prepared as follows:

The imino group in a compound corresponding to the compound of formula (IV), but in which the group R^{3a} is a hydrogen atom [which can easily be prepared by any known method (for example as described in Japanese Patent Kokai Application No. Sho 62-103088)]is protected. The protecting reaction can be conducted in a similar way to that described in Step A2(3) of Reaction Scheme A, above. The protecting group may be, for example, an acyl group, such as an alkanoyl group having from 1 to 18 carbon atoms as exemplified above. The protected compound is then allowed to react in an inert solvent (which may be, for example, a fatty acid, such as acetic acid or propionic acid, or acid anhydride, such as acetic anhydride or propionic anhydride, or a mixture of any two or more thereof) with a nitrating agent (such as fuming nitric acid or anhydrous nitric acid) at a suitable temperature, for example from 0° C. to 50° C., for a period of, for example, from 15 minutes to 5 hours, and is finally treated with an acid (such as aqueous hydrochloric acid or aqueous sulfuric acid) at a suitable temperature, for example from 20° C. to 100° C., for a period of, for example, from 15 minutes to 5 hours to remove the protecting group.

The compound of formula (III), which is the other starting material, can easily be prepared, for example by the processes shown below in Reaction Schemes B, C, D and E.

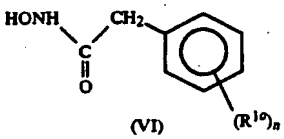
Reaction Scheme B:

-continued



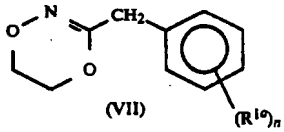
(V)

Step B1



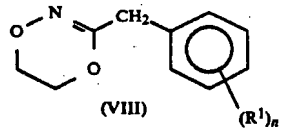
(VI)

Step B2



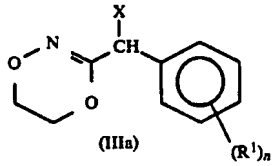
(VII)

Step B3



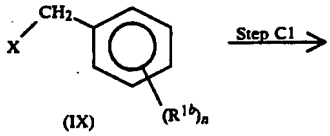
(VIII)

Step B4



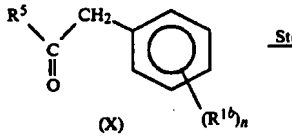
(IIIa)

Reaction Scheme C:



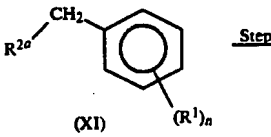
(IX)

Step C1



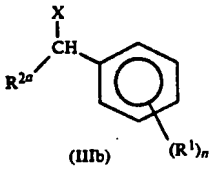
(X)

Step C2



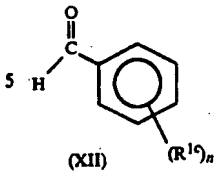
(XI)

Step C3



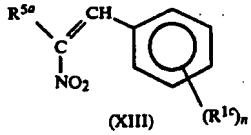
(IIIb)

Reaction Scheme D:



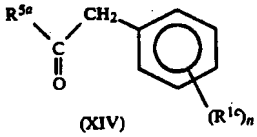
(XII)

Step D1



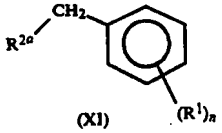
(XIII)

Step D2



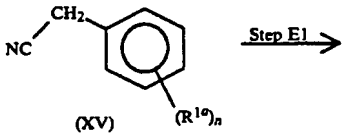
(XIV)

Step D3



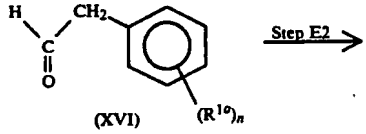
(XI)

Reaction Scheme E:



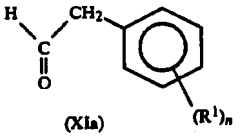
(XV)

Step E1



(XVI)

Step E2



(XIa)

In these formulae, R^1, X and n are as defined above.

R^{1a} represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an amino group, an protected alkanoyl group having from 1 to 5 carbon atoms in the alkanoyl part, a protected haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom in the haloalkanoyl part, a carbamoyl group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halo-

gen atom, or a sulfamoyl group. That is, it represents the same groups as does R^1, other than the cyano, carboxy and alkoxy. carbonyl, and the alkanoyl groups and the haloalkanoyl groups are protected.

R^{1b} represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a protected hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an protected alkanoyl group having from 1 to 5 carbon atoms in the alkanoyl part, a protected haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom in the haloalkanoyl part, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, or a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halogen atom. That is, it represents the same groups as does R^1, other than the amino, cyano, carboxy, carbamoyl, sulfamoyl and alkoxycarbonyl groups, and the alkanoyl groups, the haloalkanoyl groups and the hydroxy groups are protected.

R^{1c} represents the same groups as are defined above for R^1, except that the alkanoyl group having from 1 to 5 carbon atoms and the haloalkanoyl group having from 2 to 5 carbon atoms are protected.

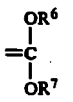
R^2a represents the same groups as are defined above for R^2, other than the dihydrodioxazinyl group.

R^4 represents an alkyl group having from 1 to 4 carbon atoms.

R^5 represents a hydrogen atom, an alkyl group having from 1 to 9 carbon atoms, a substituted alkyl group which has from 1 to 9 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined above, an alkenyl group having from 2 to 5 carbon atoms, a substituted alkenyl group which has from 2 to 5 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined above, a cycloalkyl group having from 3 to 7 carbon atoms, a substituted cycloalkyl group which has from 3 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined above, or a substituted phenyl group having at least one substituent selected from the group consisting of substituents B, defined above, and provided that any hydroxy group in substituents A is protected. That is, it represents any of the groups (other than the dihydrodioxazinyl group) defined above for R^2, but without the terminal carbonyl group.

R^{5a} represents any of the groups represented by R^5, except that the hydroxy group of substituent A need not be protected.

There is no particular limitation on the nature of the protecting group for the alkanoyl group having from 1 to 5 carbon atoms or the haloalkanoyl group having from 2 to 5 carbon atoms, and any such group commonly used for the protection of aldehydes and ketones in the field of organic chemistry. Examples include an acetal or ketal containing a carbonyl moiety as shown in the following formula:



(XVII)

in which R^6 and R^7 are the same or different and each represents an alkyl group having from 1 to 4 carbon atoms (such as a methyl, ethyl, propyl, isopropyl or butyl group) or R^6 and R^7 together form an alkylene group having 2 or 3 carbon atoms (such as an ethylene or trimethylene group). We prefer an acetal or ketal in which R^6 and R^7 are each a methyl or ethyl group, or R^6 and R^7 together form an ethylene or trimethylene group.

The nature of the hydroxy-protecting groups which may be employed in this reaction is not critical and any hydroxy-protecting group known for use in this type of reaction may equally be employed here. Examples of such groups include groups derived from the cyclic ethers, such as the tetrahydropyranyl or tetrahydrofuranyl group.

In Reaction Scheme B, a compound of formula (IIIa) is prepared; this is a compound of formula (III) in which R^2 is a dihydrodioxazinyl group.

In Step B1 of this Reaction Scheme, a compound of formula (VI) is prepared by reacting a compound of formula (V) with hydroxylamine or with a mineral acid salt of hydroxylamine (such as the hydrochloride or the sulfate) in an inert solvent (for example, an alcohol such as methanol or ethanol) and in the presence of a base (for example, an alkali metal alkoxide such as sodium methoxide, sodium ethoxide or potassium t-butoxide) at a suitable temperature, preferably from 0° C. to 150° C. (more preferably from about room temperature to 100° C.) for a suitable period, preferably from 1 to 24 hours (more preferably from 2 to 15 hours).

In Step B2 of this Reaction Scheme, a compound of formula (VII) is prepared by reacting a compound of formula (VI) with a compound of formula (XVIII):

$$X^a CH_2CH_2 X^b \qquad \text{(XVIII)}$$

in which X^a and X^b are the same or different and each represents a halogen atom. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved, and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: water, and alcohols, such as methanol or ethanol. The reaction is also preferably effected in the presence of a base, the nature of which is also not critical to the present invention. Examples of such bases include: alkali metal carbonates, such as sodium carbonate or potassium carbonate; and alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the present invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 200° C. (more preferably at a temperature from about room temperature to 150° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction

is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

Step B3 of this Reaction Scheme is optional to give a compound of formula (VIII), and may consist of one or more of the following reactions:

(1) Removal of the alkanoyl or haloalkanoyl-protecting group contained in R^{1a};

(2) Conversion of the halogen atom contained in R^{1a} into a cyano group;

(3) Conversion of the halogen atom contained in R^{1a} into a carboxy group, followed, if desired, by conversion of the carboxy group into an alkoxycarbonyl group having from 1 to 4 carbon atoms in the alkoxy moiety.

In Step B3(1) of this Reaction Scheme, removal of the alkanoyl- or haloalkanoyl-protecting group can be effected by conventional means commonly employed in the field of organic chemistry. For example, if the protecting group is an acetal or a ketal, a corresponding compound of formula (VII) is reacted with an acid (for example, a mineral acid, such as hydrochloric acid, sulfuric acid or nitric acid; or an organic acid, such as acetic acid, trifluoroacetic acid, methanesulfonic acid or p-toluenesulfonic acid). The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: water and alcohols, such as methanol or ethanol. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 100° C. (more preferably at a temperature from about room temperature to 50° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 5 hours (more preferably from 30 minutes to 2 hours) will usually suffice.

Conversion of a halogen atom into a cyano group in Step B3(2) of this Reaction Scheme is preferably effected by reacting the corresponding compound of formula (VII) with a metal cyanide, such as sodium cyanide, potassium cyanide or copper cyanide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: amides, such as dimethylformamide or dimethylacetamide; and ethers, such as diethyl ether or tetrahydrofuran. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 200° C. (more preferably at a temperature from about room temperature to 150° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

Conversion of the halogen atom into a carboxy group in Step B3(3) of this Reaction Scheme is preferably effected by reacting the corresponding compound of formula (VII) with magnesium. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether or tetrahydrofuran. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 150° C. (more preferably at a temperature from about room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice. The resulting Grignard reagent is then reacted with carbon dioxide gas at a temperature from, for example, 0° C. to 150° C. (more preferably at a temperature from about room temperature to 100° C.) for a suitable period, for example from 30 minutes to 24 hours (more preferably from 1 to 10 hours).

Conversion of the resulting carboxy group into an alkoxycarbonyl group having from 1 to 4 carbon atoms can, if desired, be conducted by reacting the corresponding carboxylic acid with an alcohol having from 1 to 4 carbon atoms, such as methanol, ethanol, propanol, isopropanol or butanol, in the presence of an acid (for example, a mineral acid, such as hydrochloric acid, sulfuric acid or nitric acid; or an organic acid, such as acetic acid, trifluoroacetic acid, methane. sulfonic acid or p-toluensulfonic acid). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 100° C. (more preferably at a temperature from about room temperature to 50° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 5 hours (preferably from 1 to 2 hours) will usually suffice. Rather than using any additional solvent, this reaction is usually carried out by using as the solvent a large excess of the alcohol having from 1 to 4 carbon atoms, which is one of the reagents.

In Step B4, a compound of formula (IIIa) is prepared by reacting a compound of formula (VIII) with a haloimide, such as N-chlorosuccimide, N-bromosuccimide or N-iodosuccimide in the presence of a radical initiator, such as benzoyl peroxide, or by reacting said compound of formula (VIII) with a halogen, such as chlorine, bromine or iodine, in an inert solvent (for example, a halogenated hydrocarbon, preferably a halogenated aliphatic hydrocarbon, such as methylene chloride, chloroform or carbon tetrachloride). The reaction can

take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 100° C. (more preferably at a temperature from about room temperature to 50° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 20 hours (more preferably from 1 to 15 hours) will usually suffice.

In Reaction Scheme C, a compound of formula (IIIb) is prepared. This is a compound of formula (III) in which R^2 is replaced by R^{2a}, that is any of the groups defined above for R^2 except a dihydrodioxazinyl group.

In Step C1 of this Reaction Scheme, a compound of formula (X) is prepared by reacting a compound of formula (IX) with magnesium in an inert solvent (for example, an ether, such as diethyl ether or tetrahydrofuran), to give a Grignard reagent. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 150° C. (more preferably at a temperature from about room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice. The resulting Grignard reagent is then reacted with a compound of formula (XIX), (XX) or (XXI):

$$R^{5b}—CN \quad (XIX)$$

$$R^{5c}—COX \quad (XX)$$

or

$$R^5—CO—O—CO—R^{5c} \quad (XXI)$$

in which R^5 and X are as defined above; R^{5b} represents any of the groups defined for R^5, except a group having a cyano substituent; and R^{5c} represents any of the groups defined for R^5, except a hydrogen atom. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 150° C. (more preferably at a temperature from about room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice.

Step C2 of Reaction Scheme C comprises one or more of the following optional reactions:

(1) Removal of the alkanoyl or haloalkanoyl-protecting group contained in R^{1b};

(2) Removal of the hydroxy-protecting group contained in R^{1b}, R^5 etc;

(3) Conversion of the halogen atom contained in R^{1b} into a cyano group, and then optionally into a carbamoyl group, and then optionally into a carboxy, and finally optionally into an alkoxycarbonyl group having from 1 to 4 carbon atoms in the alkoxy moiety;

(4) Conversion of the nitro group contained in R^{1b} into an amino group; and

(5) Conversion of the alkylthio group contained in R^{1b} into a sulfamoyl group.

Removal of the alkanoyl or haloalkanoyl-protecting group in Step C2(1) and removal of the hydroxy-protecting cyclic ether group in Step C2(2) can be conducted in a similar way to that in Step B3(1) of Reaction Scheme B, as described above.

Conversion of the halogen atom into a cyano group in Step C2(3) can be conducted in a similar way to that in Step B3(2) of Reaction Scheme B, as described above. In this reaction, it is preferred not to use as the starting material a compound of formula (X) containing a halogen atom in the substituent of R^5. If a compound containing a halogen atom in the substituent R^5 is used, conversion of this halogen atom into a cyano group is also possible.

Successive conversion of the cyano group into carbamoyl and carboxy groups can be conducted by reaction of a corresponding compound of formula (X) with an aqueous mineral acid (such as aqueous sulfuric acid, aqueous hydrochloric acid or aqueous nitric acid). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 200° C. (more preferably at a temperature from about room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice. In this reaction, it is possible to choose whether the carbamoyl or the carboxy compound will be obtained by adjusting the acid concentration. For example, the carbamoyl compound can be obtained by reaction in about 90% sulfuric acid, and then it can be converted into the carboxy compound by reaction in about 60% sulfuric acid.

Conversion of the carboxy group into an alkoxycarbonyl group having from 1 to 4 carbon atoms in the alkoxy moiety can be conducted in a similar way to that described in Step B3(3) of Reaction Scheme B, as described above.

Conversion of the nitro group into an amino group in Step C2(4) can be conducted by reacting the corresponding compound of formula (X) with hydrogen gas (preferably at from 1 atmosphere to 5 atmospheres) in an inert solvent (for example, an alcohol, such as methanol or ethanol) and in the presence of a reducing catalyst (such as Raney-nickel, palladium-on-carbon or platinum oxide). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 150° C. (preferably at room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and

solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from I to 10 hours) will usually suffice.

Conversion of the alkylthio group into a sulfamoyl group in Step C2(5) can be conducted by reacting a corresponding compound of formula (X) with a halogenating agent (such as chlorine or bromine) in an inert solvent (for example, water, an organic acid, such as acetic acid or propionic acid or a mixture of any two or more thereof), to give a sulfonyl halide. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from −10° C. to 100° C. (more preferably at from 5° C. to 50° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice. The resulting sulfonyl halide is then reacted with ammonia in an inert solvent (for example, water or an alcohol, such as methanol or ethanol) at, for example, from 0° C. to 100° C. (more preferably at room temperature to 50° C.) for a suitable period, for example from 30 minutes to 24 hours (more preferably from 1 to 10 hours).

In Step C3 of Reaction Scheme C, a compound of formula (IIIb) is prepared by halogenation of the compound of formula (XI) prepared in Step C2. This reaction is essentially the same as that described in Step B4 of Reaction Scheme B, and may be carried out using the same reagents and reaction conditions.

Reaction Scheme D provides an alternative route for preparing the compound of formula (XI), which is also prepared in Step C2 of Reaction Scheme C.

In Step D1 of Reaction Scheme D, a compound of formula (XIII) is prepared by reacting a compound of formula (XII) with a compound of formula (XXII):

$$O_2N—CH_2—R^{5a} \qquad (XXII)$$

in which R^{5a} is as defined above. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include organic acids, such as acetic acid or propionic acid. The reaction is also normally and preferably effected and in the presence of a base, for example, an ammonium salt of an organic acid, such as ammonium acetate, ammonium propionate or ammonium benzoate. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about room temperature to 200° C. (more preferably at from 50° C. to 150° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

In Step D2 of Reaction Scheme D, a compound of formula (XIV) is prepared by reacting a compound of formula (XIII) with a reducing agent (such as zinc or iron) in an inert solvent (for example, an organic acid, such as acetic acid or propionic acid) and in the presence of water. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about room temperature to 250° C. (more preferably at from 50° C. to 150° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice.

Step D3 of this Reaction Scheme is optional and comprises removal of the alkanoyl- or haloalkanoyl protecting group contained in R^{1c}. The removal reaction is essentially the same reaction as that employed in Step B3 of Reaction Scheme B, and may be carried out employing the same reagents and reaction conditions.

Reaction Scheme E provides an alternative route for preparing a compound of formula (XI), which is also prepared in Step C2 of Reaction Scheme C, when R^{2a} in the compound of formula (XI) is a formyl group, that is a compound of formula (XIa).

In Step E1 of Reaction Scheme E, a compound of formula (XVI) is prepared by reacting a compound of formula (XV) with a reducing agent [for example, an aluminum hydride, such as lithium tri(t-butoxy)aluminum hydride or lithium aluminum hydride]. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include ethers, such as diethyl ether or tetrahydrofuran. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from −30° C. to 50° C. (more preferably at from 0° C. to room temperature). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

Step E2 of Reaction Scheme E is optional and comprises one or more of the following reactions:

(1) Removal of the alkanoyl or haloalkanoyl-protecting group contained in R^{1a};

(2) Conversion of the halogen atom contained in R^{1a} into a cyano group, which may then, if desired, be converted into a carboxy group, which finally may, if desired, be converted into an alkoxycarbonyl group.

These reactions are essentially the same as those described above in relation to Step C2 of Reaction Scheme C, and may be carried out employing the same reagents and reaction conditions.

After completion of any of these reactions, the desired compound can be recovered from the reaction

mixture by conventional means. For example, insoluble matter, if any, is filtered off, and, if the reaction solution is acidic or alkaline, the solution is neutralized. The desired product can then be recovered by distilling off the solvent, or by adding water, extracting the resulting mixture with a water-immiscible organic solvent, such as ethyl acetate, drying the extract, and then distilling off the solvent. If necessary, the product thus obtained can be further purified by conventional means, such as recrystallization or the various chromatography techniques, for example preparative thin layer chromatography or column chromatography, notably column chromatography.

Alternatively, when the desired compound is a carboxylic acid derivative, it may be recovered from the reaction medium by the following procedure: making the reaction solution alkaline; extracting the resulting mixture with a water-immiscible organic solvent, such as ethyl acetate; neutralizing the aqueous layer; extracting the desired compound with a water-immiscible organic solvent, such as ethyl acetate; drying the extract; and then distilling off the solvent.

The compounds of the present invention prepared as described above may be converted to acid addition salts and/or to complexes with metal ions by methods well known in the art.

BIOLOGICAL ACTIVITY

The compounds of formula (I) and their tautomers, salts and complexes of the present invention have an excellent inhibitory activity against blood platelet aggregation, and are therefore very useful for prevention and therapy of thrombosis and embolism. These activities are demonstrated by the following Test Examples, which employ techniques well recognized in the art to provide a model of such activity in humans and other mammals.

TEST EXAMPLE 1

Prolongation of Bleeding Time in mice

Male mice of the ICR strain (supplied by Japan Charles River Inc.) were divided into groups of 10 each for the test. A sample of the drug to be tested was suspended in a 5% w/v aqueous solution of gum arabic, and administered orally to the mice at a dose of 3 mg/kg for 3 successive days, namely 48 hours, 24 hours and 4 hours before the bleeding test. For the test, each of the mice was fixed by use of conventional apparatus, and the tail was cut 5 mm from the end. The last 2 cm of the tail was soaked in physiological saline kept warm at 37° C. The time at which bleeding was observed to cease for a successive 15 seconds was regarded as the point at which bleeding stopped, and the time between cutting the tail until the point when bleeding stopped was recorded as the bleeding time. The bleeding time was observed for a maximum of 5 minutes, and, even if bleeding continued for longer than 5 minutes, the bleeding time was reported as 5 minutes (300 seconds). The results are shown in Table 2. The test was carried out using certain of the compounds of the present invention, as well as with two prior art compounds.

Each of the compounds of the present invention is identified in the Table by the number assigned to it in the foregoing Table 1 and by the number of the Example hereafter which illustrates its preparation. The prior art compounds are identified as follows:

Compound A: 5 (2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

Compound B: 5-(2-chloro-α-methoxycarbonylbenzyl) 4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

TEST EXAMPLE 2

Inhibition of Blood Platelet Aggregation

Female rats of the SD strain (supplied by Japan Charles River Inc.) were divided into groups of 4 each for the test. A sample of the drug to be tested was suspended in a 5% w/v aqueous solution of gum arabic, and administered orally to the rats 4 hours before the test. As a control, a 5% w/v aqueous solution of gum arabic was administered to a control group of rats, without any test drug. Blood platelet aggregation was tested according to the method of P. Lumley and P. P. A. Humphrey [J. Pharmacol. Methods 6, 153–166 (1981)]with a partial modification. From the abdominal aorta of the anesthetized rat, 5.4 ml of a blood sample was taken in 0.6 ml of a 3.8% (w/v) sodium citrate solution serving as an anticoagulant. The resulting citrate-containing blood samples were poured into cuvettes, with 1.2 ml in each cuvette, and stirred (1000 rpm) at 37° C. After preliminary heating for 2 minutes, 0.3 ml of the blood sample was taken out of each of the cuvettes, and the blood platelet count was measured by means of an automatic blood cell counter (E-4000, Sysmex); this was regarded as the blood platelet count before addition. 0.9 ml of the blood sample in the cuvette was then mixed with 0.1 ml of a 0.05M adenosine diphosphate (ADP) solution or with 0.1 ml of a collagen suspension (0.06 mg/ml), to induce blood platelet aggregation. Two minutes after addition of the ADP, or 4 minutes after addition of the collagen, 0.3 ml of the blood sample was taken and the blood platelet count was measured; this was regarded as the blood platelet count after addition. The blood platelet aggregation rate was calculated from the following equation.

100× (blood platelet count before addition−blood platelet count after addition)/blood platelet count before addition

The inhibitory effect was calculated as the percent inhibition of the treated groups as compared with the control groups. The results are reported in Table 2.

TABLE 2

Ex. No.	Cpd. No.	Test Ex. 1 Bleeding time (hours), 3 mg/kg	Test Ex. 2 % Inhibition 1 mg/kg	3 mg/kb	10 mg/kg
5	60	2.20	—	74.2	100
6	19	2.13	—	29.3	97.8
12	59	>2.75	57.1	98.1	—
20	235	>2.75	98.8	—	—
22	233	2.30	—	—	98.9
23	190	>2.75	100	—	—
25	194	>2.75	100	—	—
26	196	>2.75	97.6	—	—
Compound A		1.00	—	—	3.7*
Compound B		1.80	—	25.7	98.8

*at a dose of 30 mg/kg.

For therapeutic or prophylactic use, the compounds of the present invention may be administered by themselves or in admixture with any one or more conventional carriers, diluents or additives. Administration may be by any convenient route, for example orally or parenterally, and the formulation will be chosen having regard to the intended route of administration. The

compounds may, for example, be administered in the form of powders, granules, tablets, capsules and injections. The dosage may vary depending upon the severity and nature of the disorder, as well as the symptoms, age and body weight of the patient and the chosen route of administration; however, in the case of oral administration, we would normally suggest a dose of from 1 to 1000 mg, more preferably from 10 to 500 mg, if administered orally, or a dose of from 0.5 to 500 mg, more preferably from 5 to 250 mg, if administered intravenously. The compound may be administered in single or divided doses, e.g. from 1 to 3 times a day depending on the symptoms.

The preparation of the compounds of the present invention is further illustrated by the following non-limiting Examples, whilst the preparation of certain of the starting materials used in these Examples is illustrated by the subsequent Preparations.

EXAMPLE 1

5-(2-Chloro-α-trifluoroacetylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 113)

10 ml of methylene chloride were added to 0.39 g (2.6 mmole) of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride and 0.28 g (2.6 mmole) of sodium carbonate, and then a solution of 0.67 g (2.2 mmole) of 2-chloro-α-trifluoroacetylbenzyl bromide in 10 ml of methylene chloride was slowly added to the resulting mixture, whilst stirring at room temperature. The mixture was then stirred at room temperature for 3 hours. At the end of this time, 200 ml of ethyl acetate were added to the reaction mixture, and the organic layer was separated, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure, and the resulting residue was subjected to silica gel column chromatography, using a 100:4 by volume mixture of toluene and ethyl acetate as the eluent, to give 0.31 g of the title compound as a colorless oil.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1}: 1685, 1705.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.90–3.04 (2H, multiplet); 3.90 (1H, triplet, J=6.0 Hz); 4.01 (1H, triplet, J=6.0 Hz); 5.51 (1H, doublet, J=7.3 Hz); 5.58 (1H, doublet, J=7.3 Hz); 6.82 (1H, doublet, J=5.4 Hz); 7.19 (2H, doublet, J=5.4 Hz); 7.36–7.58 (4H, multiplet).

Mass spectrum (CI, m/z): 360 ($M^+ + 1$). Here and hereafter, in the mass spectra, "CI" means "chemical ionization".

EXAMPLE 2

5-[2-Chloro-α-(5,6-dihydro-1,4,2-dioxazin-3-yl) benzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 3)

2(a) Following a procedure similar to that described in Example 1, except that an equivalent amount of 2-chloro-α-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide (prepared as described in Preparation 18) was used in place of the 2-chloro-α-trifluoroacetylbenzyl bromide, the title compound was obtained as a colorless oil in a yield of 77%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.77–2.94 (4H, multiplet); 3.63 (1H, doublet, J=14.4 Hz); 3.79 (1H, doublet, J=14.4 Hz); 3.96–4.02 (1H, multiplet); 4.08–4.14 (1H, multiplet); 4.27–4.32 (1H, multiplet); 4.36–4.42 (1H, multiplet); 4.75 (1H, singlet); 6.70 (1H, doublet, J=5.4 Hz); 7.07 (1H, doublet, J=5.4 Hz); 7.20–7.90 (4H, multiplet).

Mass spectrum (CI, m/z): 349 ($M^+ + 1$).

2(b) 2.7 g of the title compound obtained as described in step (a) above were dissolved in 100 ml of diethyl ether, and hydrogen chloride gas was blown into the resulting solution at room temperature. The crystals which precipitated were collected to obtain 2.3 g of the hydrochloride of the title compound as a colorless powder, melting at 104°–107° C.

Elemental analysis: Calculated for $C_{17}H_{17}ClN_2O_2S.HCl.3/2H_2O$: C, 49.52%; H, 5.13%; N, 6.80%., Found: C, 49.81%; H, 4.73%; N, 6.56%.

EXAMPLE 3

5-[2-Fluoro-α-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl]-4,5,6,7-tetrahydrothieno]3,2-c]pyridine and its hydrochloride (Compound No. 2)

3(a) Following a procedure similar to that described in Example 1, except that an equivalent amount of 2-fluoro-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide (prepared as described in Preparation 19) was used in place of the 2-chloro-α-trifluoroacetylbenzyl bromide, the title compound was obtained as a colorless oil in a yield of 50%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.73–2.98 (4H, multiplet); 3.63 (1H, doublet, J=13.8 Hz); 3.79 (1H, doublet, J=13.8 Hz); 3.95–4.18 (2H, multiplet); 4.23–4.45 (H, multiplet); 4.61 (1H, singlet); 6.70 (1H, doublet, J TM 5.4 Hz); 7.09 (1H, doublet, J=5.4 Hz); 7.20–7.80 (4H, multiplet).

Mass spectrum (CI, m/z) : 333 ($M^+ + 1$).

3(b) The procedure described in Example 2(b) was repeated, using the title compound as prepared in step (a) above, to obtain the hydrochloride of the title compound as a colorless powder, melting at 108°–112° C., in a yield of 81%.

Elemental analysis: Calculated for $C_{17}H_{17}FN_2O_2S$ $HCl.H_2O$: C, 52 78%; H, 5.21%; N, 7.24%, Found: C, 53.19%; H, 4.99%; N, 7.16%.

EXAMPLE 4

5-[2,6-Difluoro-α-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 7)

Following a procedure similar to that described in Example 1, except that an equivalent amount of 2,6-difluoro-α- 5,6-dihydro 1,4,2-dioxazin-3-yl)benzyl bromide (prepared as described in Preparation 20) was used in place of the 2-chloro-α-trifluoroacetylbenzyl bromide, the title compound was obtained as a colorless powder, melting at 151°–153° C., in a yield of 8%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.81–2.93 (4H, multiplet); 3.62 (1H, doublet, J=14.0 Hz); 3.79 (1H, doublet, J=14.0 Hz); 4.00–4.10 (2H, multiplet); 4.26–4.36 (2H, multiplet); 4.59 (1H, singlet); 6.70 (1H, doublet, J=5.4 Hz); 7.08 (1H, doublet, J=5.4 Hz); 7.20–7.80 (4H, multiplet).

Mass spectrum (CI, m/z) : 351 ($M^+ + 1$).

Elemental analysis: Calculated for $C_{17}H_{16}F_2N_2O_2S$: C, 58.27%; H, 4.60%; N, 8.00%; Found: C, 58.22%; H, 4.61%; N, 7.79%.

EXAMPLE 5

5-(2-Chloro-α-cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its sulfate (Compound No. 60)

5(a) Following a procedure similar to that described in Example 1, except that an equivalent amount of 2-chloro-α-cyclopropylcarbonylbenzyl bromide was used in place of the 2-chloro-α-trifluoroacetylbenzyl bromide, the title compound was obtained as a yellow oil in yield of 66%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.78–0.90 (2H, multiplet); 0.96–1.06 (2H, multiplet); 2.15–2.29 (1H, multiplet); 2.83–2.94 (4H, multiplet); 3.56 (1H, doublet, J=4.3 Hz); 3.72 (1H, doublet, J=4.3 Hz); 5.06 (1H, singlet); 6.68 (1H, doublet, J=4.9 Hz); 7.06 (1H, doublet, J=4.9 Hz): 7.10–7.70 (4H, multiplet).

Mass spectrum (CI, m/z) : 332 ($M^+ + 1$), 262.

5(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound as prepared in step (a) above, except that concentrated sulfuric acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the sulfate of the title compound as white crystals, melting at 184°–186° C., in a yield of 70%.

Elemental analysis: Calculated for $C_{18}H_{18}ClNOS.H_2SO_4$: C, 50.28%; H, 4.69%; N, 3.26%.; Found: C, 50.43%; H, 4.53%; N, 2.87%.

EXAMPLE 6

5-(2-Fluoro-α-propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 19)

6(a) 1.85 g 11.13 mmole) of 1-(2-fluorophenyl)-2-butanone (prepared as described in Preparation 9) were dissolved in 30 ml of carbon tetrachloride, and then a solution of 1.78 g of bromine in 15 ml of carbon tetrachloride was added dropwise to the resulting solution at room temperature over a period of 30 minutes. The resulting mixture was then stirred at room temperature for 5 hours, after which water was added to the reaction mixture. The reaction mixture was then extracted with chloroform, and the extract was dried over anhydrous magnesium sulfate. A crude 2-fluoro-α-propionylbenzyl bromide was obtained from this extract by removal of the solvent by evaporation under reduced pressure 1.95 g (11.13 mmole) of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, 3.38 g (24.45 mmole) of anhydrous potassium carbonate and 30 ml of dimethylformamide were added to the crude product thus obtained, and the resulting mixture was stirred at room temperature for 5 hours. At the end of this time, toluene was added to the reaction mixture, and after the insolubles had been removed by filtration, the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, using a 19:1 by volume mixture of toluene and ethyl acetate as the eluent, to give 1.17 g of the title compound as a pale yellow oil.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1}: 1715.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.03 (3H, triplet, J=7.0 Hz); 2.50 (2H, quartet, J=7.0 Hz); 2.80–2.95 (4H, multiplet); 3.53 (1H, doublet, J=11.0 Hz); 3.63 (1H, doublet, J=11.0 Hz); 4.75 (1H, singlet); 6.67 (1H, doublet, J=5.7 Hz); 7.05 (1H, doublet, J=5.7 Hz); 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 304 ($M^+ + 1$), 246.

6(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the reaction mixture, to obtain the maleate of the title compound as a colorless powder, melting at 101°–103° C., in a yield of 54%.

Elemental analysis: Calculated for $C_{17}H_{18}FNOS.C_4H_4O_4.\frac{1}{2}H_2O$: C, 58.86%; H, 5.41%; N, 3.27%; Found: C, 59.19%; H, 5.33%; N, 3.19%.

EXAMPLE 7

5-(α-Acetyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 10)

7(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-chlorophenyl)-2-propanone (prepared as described in Preparation 10) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 44%.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1}: 1715.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.13 (3H, singlet); 2.70–2.95 (4H, multiplet); 3.50 (1H, doublet, J=10.0 Hz); 3.70 (1H, doublet, J=10.0 Hz); 4.93 (1H, singlet); 6.65 (1H, doublet, J=5.7 Hz); 7.05 (1H, doublet, J=5.7 Hz); 7.10–7.75 (4H, multiplet).

Mass spectrum (CI, m/z) : 306 ($M^+ + 1$), 262.

7(b) A procedure similar to that described in Example (b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as a pale yellow powder, melting at 98°–101° C., in a yield of 70%.

Elemental analysis: Calculated for $C_{16}H_{16}ClNOS.HCl.\frac{1}{4}H_2O$: C, 54.70%; H, 5.16%; N, 3.98%; Found: C, 55.09%; H, 4.97%; N, 3.80%.

EXAMPLE 8

5-(2-Chloro-α-propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 20)

8(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of (2-chlorophenyl)-2-butanone (prepared as described in Preparation 11) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 32%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.05 (3H, triplet, J=6.5 Hz); 2.31–2.58 (2H, multiplet); 2.75–3.00 (4H, multiplet); 3.48 (1H, doublet, J=14.5 Hz); 3.68 (1H, doublet, J=14.5 Hz); 4.97 (1H, singlet); 6.65 (1H, doublet, J=6.0 Hz); 7.05 (1H, doublet, J=6.0 Hz); 7.10–7.65 (4H, multiplet).

Mass spectrum (CI, m/z) : 320 ($M^+ + 1$).

8(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as a pale yellow powder, melting at 110°–115° C., in a yield of 25%.

Elemental analysis: Calculated for $C_{17}H_{18}ClNOS.HCl.H_2O$: C, 54.55%; H, 5.92%; N, 3.74%; Found: C, 54.39%; H, 5.59%; N, 3.73%.

EXAMPLE 9

5-(2-Chloro-α-hexanoylbenzyl)-4,5,6,7,-tetrahydrothieno[3,2-c]pyridine (Compound No. 125)

Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-chlorophenyl)-2-heptanone (prepared as described in Preparation 12) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a yellow oil in a yield of 10%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.90 (3H, triplet, J=7.6 Hz); 1.10–1.60 (6H, multiplet); 2.40 (2H, triplet, J=8.0 Hz); 2.75–3.00 (4H, multiplet); 3.50 (1H, doublet, J=14.5 Hz); 3.70 (1H, doublet, J=14.5 Hz); 5.00 (1H, singlet); 6.65 (1H, doublet, J=6.0 Hz); 7.05 (1H, doublet, J=6.0 Hz); 7.10–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 362 ($M^+ + 1$), 262.

EXAMPLE 10

5-(α-Acetyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 9)

10(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-fluorophenyl)-2-propanone was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 55%.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1}: 1715.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.18 (3H, singlet); 2 80–2.95 (4H, multiplet); 3.55 (1H, doublet, J=12.0 Hz); 3.65 (1H, doublet, J=12.0 Hz); 4.72 (1H, singlet); 6.65 (1H, doublet, J=5.5 Hz); 7.05 (1H, doublet, J=5.5 Hz); 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 290 ($M^+ + 1$), 246.

10(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a pale yellow powder, melting at 104°–106° C., in a yield of 61%.

Elemental analysis: Calculated for $C_{16}H_{16}FNOS.C_4H_4O_4.\frac{1}{2}H_2O$: C, 57.96%; H, 5.10%; N, 3.38%; Found: C, 58.36%; H, 4.94%; N, 3.39%.

EXAMPLE 11

5-(α-Cyclobutylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 106)

11(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of cyclobutyl-2-fluorobenzyl ketone (prepared as described in Preparation 13 was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 24%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.70–2.55 (6H, multiplet); 2.80–3.00 (4H, multiplet); 3.50 (1H, doublet, J=11.0 Hz); 3.62 (1H, doublet, J=11.0 Hz); 3.70–3.90 (1H, multiplet); 4.73 (1H, singlet); 6.65 (1H, doublet, J=6.0 Hz): 7.05 (1H, doublet, J=6.0 Hz); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z) : 330 ($M^+ + 1$), 246.

11(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a colorless powder, melting at 99°–104° C., in a yield of 57%.

Elemental analysis: Calculated for $C_{16}H_{16}FNOS.C_4H_4O_4.\frac{1}{2}H_2O$: C, 60.78%; H, 5.54%; N, 3.08%; Found: C, 60.97%; H, 5.48%; N, 2.94%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.70–2.30 (6H, multiplet); 3.10–3.30 (4H, multiplet); 3.68–3.82 (1H, multiplet); 4.30 (2H, broad singlet); 5.55 (1H, singlet); 6.30 (2H, singlet); 6.72 (1H, doublet, J=6.5 Hz); 7.20 (1H, doublet, J=6.5 Hz); 7.25–7.60 (4H, multiplet).

EXAMPLE 12

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 59)

12(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of cyclopropyl 2-fluorobenzyl ketone (prepared as described in Preparation 8) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a colorless oil in a yield of 69%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.78–0.90 (2H, multiplet); 0.98–1.11 (2H, multiplet); 2.22–2.34 (1H, multiplet); 2.72–2.98 (4H, multiplet); 3.58 (1H, doublet, J=4.2 Hz); 3.68 (1H, doublet, J=4.2 Hz); 4.85 (1H, singlet); 6.68 (1H, doublet, J=4.9 Hz); 7.06 (1H, doublet, J=4.9 Hz); 7.20–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 316 ($M^+ + 1$), 246.

12(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 171°–173° C., in a yield of 75%.

Elemental analysis: Calculated for $C_{18}H_{18}FNOS.HCl$: C, 61.44%; H, 5.44%; N, 3.98%, Found: C, 61.37%; H, 5.74%; N, 3.85%.

EXAMPLE 13

5-(α-Butyryl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 116)

13(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-fluorophenyl)-2-pentanone (prepared as described in Preparation 5) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 41%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.82 (3H, triplet, J=9.5 Hz); 1.45–1.70 (2H, multiplet); 2.41 (2H, triplet, J=8.0 Hz); 2.75–2.95 (4H, multiplet); 3.55 (1H, doublet, J=13.0 Hz); 3.62 (1H, doublet, J=13.0 Hz); 4.75 (1H, singlet); 6.65 (1H, doublet, J=6.0 Hz); 7.05 (1H, doublet, J=6.0 Hz): 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 318 ($M^+ + 1$), 246.

13(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a colorless powder, melting at 89°–90° C., in a yield of 36%.

Elemental analysis: Calculated for $C_{18}H_{20}FNOS.C_4H_4O_4$: C, 60.96%; H, 5.58%; N, 3.23%; Found: C, 60.69%; H, 5.43%; N, 3.01%.

EXAMPLE 14

5-(2-Fluoro-α-valerylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 120)

14(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-fluorophenyl)-2-hexanone (prepared as described in Preparation 6) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 46%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.83 (3H, triplet, J=8.0 Hz); 1.12–1.35 (2H, multiplet); 1.40–1.70 (2H, multiplet); 2.45 (2H, triplet, J=8.2 Hz); 2.60–2.90 (4H, multiplet); 3.52 (1H, doublet, J=14.0 Hz); 3.65 (1H, doublet, J=14.0 Hz); 4.75 (1H, singlet); 6.65 (1H, doublet, J=6.0 Hz); 7.05 (1H, doublet, J=6.0 Hz); 7.10–7.50 (4H, multiplet).

Mass Spectrum (CI, m/z) : 332 ($M^+ + 1$), 246.

14(b) A procedure similar to that described in Example (b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a colorless powder, melting at 92°–93° C., in a yield of 26%.

Elemental analysis: Calculated for $C_{19}H_{22}FNOS.C_4H_4O_4$: C, 61.73%; H, 5.86%; N, 3.13%; Found: C, 61.38%; H, 5.88%; N, 2.59%.

EXAMPLE 15

5-(2-Fluoro-α-pivaloylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 122)

15(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-fluorophenyl)-3,3-dimethyl-2-butanone (prepared as described in Preparation 7) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 87%.

Nuclear Magnetic Resonance Spectrum (CDCl3) δ ppm: 1.10 (9H, singlet); 2.74–3.00 (4H, multiplet); 3.55 (1H, doublet, J=15.0 Hz); 3.66 (1H, doublet, J=15.0 Hz); 5.23 (1H, singlet); 6.63 (1H, doublet, J=6.0 Hz); 7.03 (1H, doublet, J=6.0 Hz); 7 10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 332 ($M^+ + 1$), 246.

15(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as a pale yellow powder, melting at 85°–90° C., in a yield of 34%.

Elemental analysis: Calculated for $C_{19}H_{22}FNOS.HCl.H_2O$: C, 59.14%; H, 6.23%; N, 3.63%; Found: C, 58.99%; H, 6.57%; N, 3.17%.

EXAMPLE 16

5-[2-Chloro-α-(4-fluorobenzoyl)benzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 149)

16(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 2-chlorobenzyl 4-fluorophenyl ketone (prepared as described in Preparation 22) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 58%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2 80–3.00 (4H, multiplet); 3.63 (1H, doublet, J=16.0 Hz); 3.80 (1H, doublet, J=16.0 Hz); 5.80 (1H, singlet); 6.63 (1H, doublet, J=6.0 Hz); 7.00–7.60 (6H, multiplet); 7.95–8.15 (2H, multiplet).

Mass spectrum (CI, m/z) : 386 ($M^+ + 1$), 262.

16(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as a yellowish brown powder, melting at 121°–130° C., in a yield of 40%.

Elemental analysis: Calculated for $C_{21}H_{17}ClFNOS.HCl.\frac{1}{2}H_2O$: C, 58.47%; H, 4.44%; N, 3.25%; Found: C, 58.25%; H, 4.86%; N, 3.48%.

EXAMPLE 17

5-(2-Fluoro-α-isobutyrylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 118)

17(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 2-fluorobenzyl isopropyl ketone (prepared as described in Preparation 23) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a yellow oil in a yield of 44%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.95 (3H, doublet, J=7.0 Hz); 1.10 (3H, doublet, J=7.0 Hz); 2.60–2.80 (1H, multiplet); 2.80–2.95 (4H, multiplet); 3.50 (1H, doublet, J=11.0 Hz); 3.65 (1H, doublet, J=11.0 Hz); 4.90 (1H, singlet); 6.65 (1H, doublet, J=5.7 Hz); 7.05 (1H, doublet, J=5.7 Hz); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z) : 318 ($M^+ + 1$), 246.

17(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a colorless powder, melting at 96°–98° C., in a yield of 42%.

Elemental analysis: Calculated for $C_{18}H_{20}FNOS.C_4H_4O_4$: C, 61.02%; H, 5.59%; N, 3.23%; Found: C, 60.74%; H, 5.52%; N, 3.23%.

EXAMPLE 18

5(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 175)

18(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of cyclopropyl 2-fluorobenzyl ketone (prepared as described in Preparation 8) was used in place of the 1-(2-fluorophenyl)-2-butanone and that 2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (prepared as described in Preparation 24) was used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, the title compound was obtained as a brown oil in a yield of 72%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.82–0.92 (2H, multiplet); 1.01–1.11 (2H, multiplet); 2.00–2.20 (1H, multiplet); 2.75–3.05 (4H, multiplet); 3.61 (2H, singlet); 4.91 (1H, singlet); 7.10–7.45 (4H, multiplet); 7.55 (1H, singlet).

Mass spectrum (CI, m/z) : 361 ($M^+ + 1$), 291.

18(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 161°–168° C., in a yield of 79%.

Elemental analysis: Calculated for $C_{18}H_{17}FN_2O_3S.HCl$: C, 54.47%; H, 4.57%; N, 7.06%. Found: C, 54.47%; H, 4.63%; N, 6.89%.

EXAMPLE 19

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrofuro[3,2-c]pyridine and its hydrochloride (Compound No. 168)

19(a) Following a procedure similar to that described in Example 12, except that an equivalent amount of 4,5,6,7-tetrahydrofuro[3,2.-c]pyridine (prepared as described in Preparation 25) was used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, the title compound was obtained as a brown oil in a yield of 21%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.75–0.95 (2H, multiplet); 0.98–1.10 (2H, multiplet); 2.15–2.31 (1H, multiplet); 2.65–3.05 (4H, multiplet); 3.40–3.60 (2H, multiplet); 4.90 (1H, singlet); 6.15 (1H, doublet, J=5.0 Hz); 7.05–7.55 (5H, multiplet).

Mass spectrum (CI, m/z) : 300 ($M^+ + 1$), 230.

19(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 154°–155° C., in a yield of 39%.

Elemental analysis: Calculated for $C_{18}H_{18}FNO_2.HCl$: C, 64.38%; H, 5.70%; N, 4.17%; Found: C, 64.37%; H, 5.80%; N, 4.19%.

EXAMPLE 20

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 235)

20(a) Following a procedure similar to that described in Example 12, except that an equivalent amount of 2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2.-c]pyridine hydrochloride was used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, the title compound was obtained as a brown oil in a yield of 32%. Diisopropyl ether was added to this compound to cause crystallization, yielding white crystals, melting at 123°–125° C.

The resulting 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 235) is believed to contain a small quantity of the tautomeric 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 188), from which it was not separated.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.75–0.96 (2H, multiplet); 0.99–1.14 (2H, multiplet); 1.83–2.01 (1H, multiplet); 2.02–2.17 (1H, multiplet); 2.25–2.45 & 2.47–2.62 (together 2H, each multiplet); 2.85 & 3.10 (together 2H, each doublet, J=12.0 Hz); 3.88–4.01 & 4.03–4.16 (together 2H, each multiplet); 4.85 & 4.89 (together 1H, each singlet); 6.03 & 6.06 (together 1H, each singlet); 7.10–7.45 (4H, multiplet).

Mass spectrum (CI, m/z) : 332 ($M^+ + 1$), 262.

Elemental analysis: Calculated for $C_{18}H_{18}FNO_2S$: C, 65.23%; H, 5.48%; N, 4.23%; Found: C, 65.09%; H, 5.55%; N, 4.20%.

20 (b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 104°–109° C., in a yield of 46%.

EXAMPLE 21

5-(2-Fluoro-α-propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 234)

21(a) Following a procedure similar to that described in Example 20, except that an equivalent amount of 1-(2-fluorophenyl)-2-butanone (prepared as described in Preparation 9) was used in place of the cyclopropyl 2-fluorobenzyl ketone, the title compound was obtained as a brown oil in a yield of 36%.

The resulting 5-(2-fluoro-α-propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 234) is believed to contain a small quantity of the tautomeric 5-(2-fluoro-α-propionylbenzyl)-2-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 187).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.00 (3H, triplet, J=9.1 Hz); 1.82–1.98 (1H, multiplet); 2.25–2.50 (4H, multiplet); 2.85 & 3.05 (together 2H, each doublet, J=14.0 Hz); 3.84–3.95 & 4.04–4.17 (together 2H, each multiplet); 4.72 & 4.76 (together 1H, each singlet); 6.03 & 6.07 (together 1H, each singlet); 7.15–7.40 (4H, multiplet).

Mass spectrum (CI, m/z) : 320 ($M^+ + 1$), 262.

21(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 110°–115° C. in a yield of 78%.

EXAMPLE 22

5-(2-Chloro-α-cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 233)

Following a procedure similar to that described in Example 5, except that an equivalent amount of 2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrochloride was used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, a yellow oil was obtained. The oil was crystallized from diisopropyl ether to give the title compound as pale brown crystals, melting at 119°–123° C. in a yield of 8%.

The resulting 5-(2-chloro-α-cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 233) is believed to contain a small quantity of the tautomeric 5-(2-chloro-α-cyclopropylcarbonylbenzyl)-2-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 186).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.75–1.10 (4H, multiplet); 175–2.10 (2H, multiplet); 2.25–2.70 (2H, multiplet); 2.90–3.30 (2H, multiplet); 3.75–4.20 (2H, multiplet); 5.09 & 5.10 (together 1H, each singlet); 5.98 & 6.07 (together 1H, each singlet); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z) : 348 ($M^+ + 1$), 278.

EXAMPLE 23

2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 190)

2.6 g (7.8 mmole) of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine pyridine (prepared as described in Example 20) were dissolved in a mixture of 10 ml of dimethylformamide and 5 ml of acetic anhydride, and then 0.35 g (8.6 mmole) of a 60% w/w dispersion of sodium hydride in mineral oil was added to the resulting solution, whilst ice-cooling; the mixture was then stirred for 20 minutes at the same temperature, after which it was stirred for a further 3 hours at room temperature. At the end of this time, 300 ml of ethyl acetate were added to the mixture, which was then washed four times, each time with 50 ml of a saturated aqueous solution of sodium chloride The organic layer was separated and dried over anhydrous sodium sulfate, and the solvent was removed by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, using a 100:3 by volume mixture of toluene and ethyl acetate as the eluent, to give a yellow oil. This oil was crystallized from diisopropyl ether, to obtain the title compound as white crystals, melting at 120°–121.5° C., in a yield of 65%.

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}: 1758, 1704.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.80–0.95 (2H, multiplet); 0.99–1.16 (2H, multiplet); 2.27 (3H, singlet); 2.21–2.34 (1H, multiplet); 2.70–2.95 (4H, multiplet); 3.47 (1H, doublet, J=15.0 Hz); 3.57 (1H, doublet, J=15.0 Hz); 4.83 (1H, singlet); 6.27 (1H, singlet); 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 374 ($M^+ + 1$), 304.

Elemental analysis: Calculated for $C_{20}H_{20}FNO_3S$: C, 64.32%; H, 5.40%; N, 3.75%; Found: C, 64.46%; H, 5.39%; N, 3.73%.

EXAMPLE 24

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 192)

Following a procedure similar to that described in Example 23, except that an equivalent amount of propionic anhydride was used in place of the acetic anhydride, the title compound was obtained as white crystals, melting at 101°–102° C., in a yield of 16%.

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}: 1705, 1760.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.75–0.90 (2H, multiplet); 0.90–1.10 (2H, multiplet); 1.21 (3H, triplet, J=6.7 Hz); 2.15–2.37 (1H, multiplet); 2.55 (2H, quartet, J=6.7 Hz); 2.65–2.95 (4H, multiplet); 3.40–3.60 (2H, multiplet); 4.80 (1H, singlet); 6.25 (1H, singlet); 7.05–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 388 ($M^+ + 1$), 318.

Elemental analysis: Calculated for $C_{21}H_{22}FNO_3S$: C, 65.10%; H, 5.72%; N, 3.61%; Found: C, 64.80%; H, 5.72%; N, 3.61%.

EXAMPLE 25

2-Butyryloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 194)

Following a procedure similar to that described in Example 23, except that an equivalent amount of butyric anhydride was used in place of the acetic anhydride, the title compound was obtained as white crystals, melting at 84°–85° C., in a yield of 39%.

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}: 1756, 1706.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.75–1.10 (7H, multiplet); 165–1.85 (2H, multiplet); 2.21–2.34 (1H, multiplet); 2.49 (2H, triplet, J=7.0 Hz); 2.70–3.00 (4H, multiplet); 3.52 (2H, broad triplet, J=16.0 Hz); 4.82 (1H, singlet); 6.25 (1H, singlet): 7.05–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 402 ($M^+ + 1$), 332.

Elemental analysis: Calculated for $C_{22}H_{24}FNO_3S$: C, 65.81%; H, 6.03%; N, 3.49%. Found: C, 65.92%; H, 5.91%; N, 3.41%.

EXAMPLE 26

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 196)

Following a procedure similar to that described in Example 23, except that an equivalent amount of pivalic anhydride was used in place of the acetic anhydride, the title compound was obtained as white crystals, melting at 91°–94° C., in a yield of 44%.

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}: 1749, 1700.

Nuclear Magnetic Resonance Spectrum ($CDC_{;3}$) δ ppm: 0.79–0.92 (2H, multiplet); 0.98–1.09 (2H, multiplet); 1.31 (9H, singlet); 2.23–2.36 (1H, multiplet); 2.70–2.95 (4H, multiplet); 3.47 (1H, doublet, J=14.5 Hz); 3.58 (1H, doublet, J=14.5 Hz); 4.83 (1H, singlet); 6.26 (1H, singlet); 7.05–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 416 ($M^+ + 1$), 346.

Elemental analysis: Calculated for $C_{23}H_{26}FNO_3S$: C, 66.48%; H, 6.31%; N, 3.37%; Found: C, 66.21%; H, 6.40%; N, 3.38%.

EXAMPLE 27

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-nonanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 199)

1.0 g (3.0 mmole) of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (prepared as described in Example 20) was dissolved in 15 ml of dimethylformamide, and then 0.18 g (4.5 mmole) of a 60% w/w dispersion of sodium hydride in mineral oil and 0.82 ml (4.5 mmole) of nonanoyl chloride were added, in that order, to the resulting mixture, whilst ice-cooling. The resulting reaction mixture was then stirred at the same temperature for 30 minutes, after which it was stirred at room temperature for a further 5 hours. 300 ml of ethyl acetate were then added to the mixture, which was then washed with a saturated aqueous solution of sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, in that order. The organic layer was separated and dried over anhydrous sodium sulfate, and the solvent was removed by evaporation under reduced pres-

sure. The resulting residue was subjected to silica gel column chromatography, using a 100:2 by volume mixture of toluene and ethyl acetate as the eluent, to give a yellow oil. The oil was crystallized from petroleum ether to obtain the title compound as white crystals, melting at 45°–48° C., in a yield of 40%.

Nuclear Magnetic Resonance Spectrum (CDCl3) δ ppm: 0.80–1.80 (19H, multiplet); 2.21–2.32 (1H, multiplet); 2.53 (2H, triplet, J=7.5 Hz); 2.70–2.95 (4H, multiplet); 3.48 (1H, doublet, J=15.0 Hz); 3.57 (1H, doublet, J=15.0 Hz); 4.84 (1H, singlet); 6.27 (1H, singlet); 7.05–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 472 ($M^+ + 1$), 402.

Elemental analysis: Calculated for $C_{27}H_{34}FNO_3S$: C, 68.76%; H, 7.27%; N, 2.97%.: Found: C, 68.56%; H, 7.49%; N, 2.97%.

EXAMPLE 28

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-decanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 200)

28(a) Following a procedure similar to that described in Example 27, except that an equivalent amount of decanoyl chloride was used in place of the nonanoyl chloride, the title compound was obtained as a yellow oil in a yield of 40%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.80–1.80 (21H, multiplet); 2.18–2.32 (1H, multiplet); 2.52 (2H, triplet, J=7.5 Hz); 2.70–2.97 (4H, multiplet); 3.50 (1H, doublet, J=14.5 Hz); 3.59 (1H, doublet, J=14.5 Hz); 4.85 (1H, singlet); 6.26 (1H, singlet); 7.20–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 486 ($M^+ + 1$), 416.

28(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that diisopropyl ether was used as a solvent in place of the diethyl ether, to give the hydrochloride of the title compound as yellow crystals, melting at 62°–64° C., in a yield of 81%

Elemental analysis: Calculated for $C_{28}H_{36}FNO_3S.HCl$: C, 64.41%; H, 7.14%; N, 2.68%; Found: C, 64.12%; H, 7.05%; N, 2.63%.

EXAMPLE 29

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-palmitoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 201)

Following a procedure similar to that described in Example 27, except that an equivalent amount of palmitoyl chloride was used in place of the nonanoyl chloride, the title compound was obtained as white crystals, melting at 6620 -68° C., in a yield of 21%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.80–1.80 (33H, multiplet); 2.20–2.32 (1H, multiplet); 2.51 (2H, triplet, J=7.5 Hz); 2.70–2.95 (4H, multiplet); 3.48 (1H, doublet, J=15.0 Hz); 3.58 (1H, doublet, J=15.0 Hz); 4.84 (1H, singlet); 6.26 (1H, singlet); 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z) : 570 ($M^+ + 1$), 500.

Elemental analysis: Calculated for $C_{34}H_{48}FNO_3S$: C, 71.66%; H, 8.49%; N, 2.46%; Found: C, 71.72%; H, 8.62%; N, 2.43%.

EXAMPLE 30

2-t-Butoxycarbonyloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 203)

Following a procedure similar to that described in Example 23, except that an equivalent amount of di-t-butyl dicarbonate was used in place of the acetic anhydride, the title compound was obtained as white crystals, melting at 98°–99° C., in a yield of 15%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.80–0.90 (2H, multiplet); 0.98–1.09 (2H, multiplet); 1.55 (9H, singlet); 2.20–2.34 (1H, multiplet); 2.70–2.95 (4H, multiplet); 3.40–3.60 (2H, multiplet); 4.83 (1H, singlet); 6.27 (1H, singlet); 7.07–7.52 (4H, multiplet).

Mass spectrum (CI, m/z) : 432 ($M^+ + 1$), 362.

Elemental analysis: Calculated for $C_{23}H_{26}FNO_4S$: C, 64.02%; H, 6.07%; N, 3.25%; Found: C, 63.57%; H, 6.03%; N, 3.27%.

EXAMPLE 31

2-Amino-5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 177)

5 ml of hydrochloric acid were added to 0.4 g of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (prepared as described in Example 18), and then 0.23 g of tin powder was added to the resulting mixture, whilst stirring, after which the mixture was stirred at room temperature for a further hour. 10 ml of water were added to the reaction mixture, which was then extracted with methylene chloride. The methylene chloride layer was removed, and the aqueous layer was concentrated to dryness by evaporation under reduced pressure, and then crystallized from diethyl ether, to give a complex of the title compound with stannic chloride as a pale yellow powder in a yield of 72%.

Nuclear Magnetic Resonance Spectrum (CD_3OD) δ ppm: 0.95–1.05 (2H, multiplet); 1.20–1.35 (2H, multiplet); 1.85–1.99 (1H, multiplet); 3.60–3.80 (2H, multiplet); 6.07 (1H, singlet); 7.35–7.80 (4H, multiplet).

EXAMPLE 32

2-Acetylamino-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 179)

1.85 g (5.13 mmole) of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (prepared as described in Example 18) were dissolved in a mixture of 20 ml of acetic acid and 2 ml of acetic anhydride, and then 1.85 g of iron powder were added to the solution, whilst stirring at room temperature; the mixture was then stirred at the same temperature for 90 minutes. At the end of this time, water and chloroform were added to the reaction mixture, and the mixture was neutralized with sodium carbonate. The inorganic salt thus precipitated was filtered off, the remaining organic layer was separated and the aqueous layer was extracted with chloroform. The organic layer and the extract were combined and dried over anhydrous magnesium sulfate, and then the solvent was removed by distillation under reduced pressure. The resulting residue was then subjected to silica gel column chromatography, using a 6:4 by volume mixture of

toluene and ethyl acetate as the eluent, to give 1.86 g of the title compound. This was crystallized from diisopropyl ether to obtain 1.37 g of the title compound as white crystals, melting at 155°–159° C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.78–0.94 (2H, multiplet); 0.98–1.12 (2H, multiplet); 2.17 (3H, singlet); 2.15–2.32 (1H, multiplet); 2.70–2.99 (4H, multiplet); 3.50 (1H, doublet, J=11.4 Hz); 3.60 (1H, doublet, J=11.4 Hz); 4.86 (1H, singlet); 6.27 (1H, singlet); 7.10–7.5S (4H, multiplet); 7.80–8.00 (1H, broad singlet).

Mass spectrum (CI, m/z) : 373 ($M^+ + 1$), 303.

Elemental analysis: Calculated for $C_{20}H_{21}FN_2O_2S$: C, 64.49%; H, 5.68%; N, 7.52%.; Found: C, 64.38%; H, 5.50%; N, 7.38%.

EXAMPLE 33

2-Butyrylamino-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 181)

Following a procedure similar to that described in Example 32, except that equivalent amounts of butyric acid and butyric anhydride were used in place of the acetic acid and acetic anhydride, the title compound was obtained as white crystals, melting at 154°–157° C., in a yield of 61%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.78–0.94 (2H, multiplet); 0.90–1.10 (5H, multiplet); 1.65–1.82 (2H, multiplet); 2.21–2.39 (3H, multiplet); 2.69–2.95 (4H, multiplet); 3.47 (1H, doublet, J=11.4 Hz); 3.56 (1H, doublet, J=11.4 Hz); 4.81 (1H, singlet); 6.25 (1H, singlet); 7.10–7.60 (4H, multiplet); 7.70 (1H, singlet).

Mass spectrum (CI, m/z) : 401 ($M^+ + 1$), 331.

Elemental analysis: Calculated for $C_{22}H_{25}FN_2O_2$: C, 65.97%; H, 6.29%; N, 6.99%; Found: C, 65.95%; H, 6.36%; N, 6.95%.

EXAMPLE 34

Optically active 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 59)

0.3 g of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (prepared as described in Example 12) was separated into fractions by liquid chromatography [column: DAICEL CHIRALPAC AD (trade name), 1 cm×25 cm); eluent: a 1000:40:1 by volume mixture of hexane, isopropanol and diethylamine; column temperature: 35° C.; flow rate: 4 ml/minute], to obtain an optically active isomer A [retention time: 8.3 minutes; specific rotation angle $[\alpha]_D^{25}$: 109.4° (C=1.80, $CHCl_3$)] and an isomer B [retention time: 9.9 minutes; specific rotation angle $[\alpha]_D^{25}$:100.1° (C=1.90, $CHCl_3$)].

Isomers A and B were separately dissolved in diethyl ether, and then hydrogen chloride gas was allowed to act upon the resulting solutions to obtain 0.13 g and 0.12 g of the hydrochlorides of isomer A and isomer B, respectively, as white crystals.

Hydrochloride of isomer A

melting at 106°–110° C.

Elemental analysis: Calculated for $C_{18}H_{18}FNOS.HCl.\frac{3}{4}H_2O$: C, 59.17%; H, 5.65%; N, 3.83%; Found: C, 59.06%; H, 5.74%; N, 3.90%.

Hydrochloride of isomer B

melting at 105°–110° C.

Elemental analysis: Calculated for $C_{18}H_{18}FNOS.HCl.\frac{1}{2}H_2O$: C, 59.91%; H, 5.59%; N, 3.88%; Found: C, 59.80%; H, 5.84%; N, 3.79%.

EXAMPLE 35

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2c-]pyridine (Compound No. 207)

1.0 g (3.0 mmole) of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno [3,2-c]pyridine (prepared as described in Example 20) was dissolved in 20 ml of dimethylformamide, and then 100 mg (0.6 mmole) of potassium iodide and 0.13 g (3.3 mmole) of a 60% dispersion of sodium hydride in mineral oil were added to the solution at room temperature; the mixture was then stirred at the same temperature for 10 minutes. At the end of this time, a solution of 0.43 ml (3.0 mmole) of pivaloyloxymethyl chloride in 5 ml of dimethylformamide was added dropwise to the resulting mixture over a period of 10 minutes, and the resulting mixture was stirred at room temperature for 30 minutes. 300 ml of ethyl acetate were added to the reaction mixture, and the mixture was washed three times, each time with 50 ml of a saturated aqueous solution of sodium hydrogen. carbonate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, using a 100:3 by volume mixture of toluene and ethyl acetate as the eluent, to give the title compound as a colorless oil in a yield of 15%.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1}: 1715, 1702.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.79–0.93 (2H, multiplet); 0.99–1.14 (2H, multiplet); 1.22 (9H, singlet); 2.18–2.31 (1H, multiplet); 2.65–2.95 (4H, multiplet); 3.44 (1H, doublet, J=15.5 Hz); 3.55 (1H, doublet, J=15.5 Hz); 4.84 (1H, singlet); 5.57 (2H, singlet); 6.04 (1H, singlet); 7.05–7.50 (4H, multiplet).

Mass spectrum (CI, m/z) : 446 ($M^+ + 1$), 376.

EXAMPLE 36

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-methoxy-4,5,6,7-tetrahydrothieno[3,2c]pyridine and its hydrochloride (Compound No. 210)

36(a) A procedure similar to that described in Example 35 was repeated, except that an equivalent amount of methyl iodide was used in place of the pivaloyloxymethyl chloride and potassium iodide, to give the title compound as a yellow oil in a yield of 45%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.80–0.92 (2H, multiplet); 1.00–1.10 (2H, multiplet); 2.20–2.36 (1H, multiplet); 2.65–2.96 (4H, multiplet); 3.42 (1H, doublet, J=14.5 Hz); 3.55 (1H, doublet, J=14.5 Hz); 3.80 (3H, singlet); 4.82 (1H, singlet); 5.80 (1H, singlet);

7.10–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 346 ($M^+ + 1$), 276.

36(b) Following a procedure similar to that described in Example 2(b), using the whole of the title compound prepared as described in step (a) above, the hydrochloride of the title compound was obtained as white crystals, melting at 102°–106° C., in a yield of 78%.

Elemental analysis:

Calculated for $C_{19}H_{20}FNO_2S.HCl.\frac{1}{2}H_2O$: C, 58.38%; H, 5.67%; N, 3.58%.; Found: C, 58.08%; H, 5.77%; N, 3.53%.

EXAMPLE 37

5-[α-(2-Fluorocyclopropylcarbonyl-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 275)

Following a procedure similar to that described in Example 1, except that equivalent amounts of 2-oxo2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrochloride and 2-fluoro-α-(2-fluorocyclopropylcarbonyl)-benzyl bromide (prepared as described in Preparation 27) were used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride and 2-chloro-α-trifluoroacetylbenzyl bromide, the title compound was obtained as a yellow oil in a yield of 31%.

The resulting 5-[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 275) is believed to contain a small quantity of the tautomeric 5-[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-2-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 274), from which it was not separated.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1}: 1680.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.48–1.55 (2H, multiplet); 1.85–2.01 (1H, multiplet); 2.30–2.51 (2H, multiplet); 2.53–2.90 (1H, multiplet); 3.00–3.20 (2H, multiplet); 3.83–4.01 & 4.03–4.18 (together 2H, each multiplet); 4.46–4.60 & 4.79–4.92 (together 2H, each multiplet); 6.05 & 6.09 (together 1H, each singlet); 7.10–7.45 (4H, multiplet). Mass spectrum (CI, m/z) : 350 ($M^+ + 1$), 262.

PREPARATION 1

3-(2-Chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine

A solution of 5.0 g (29.3 mmole) of o-chlorophenylacetic acid and 0.3 g of p-toluenesulfonic acid monohydrate in 50 ml of methanol was heated under reflux for 6 hours. At the end of this time, 3.1 g (44 mmole) of hydroxylamine hydrochloride were added to the reaction mixture, followed by 2.1 g of sodium methoxide. The resulting reaction mixture was then heated under reflux for 10 hours. 14.2 g (103 mmole) of potassium carbonate and 5.1 ml of 1,2-dibromoethane were then added to the resulting reaction mixture, followed by 15 ml of water. The reaction mixture was then heated under reflux for a further 10 hours. At the end of this time, 200 ml of ethyl acetate were added to the reaction mixture, and the organic layer was separated, washed with a saturated aqueous solution of sodium hydrogencarbonate and dried over anhydrous sodium sulfate; the solvent was then removed by distillation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 9:1 by volume mixture of toluene and ethyl acetate as the eluent, to give 4.9 g of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.67 (2H, singlet); 4.05 (2H, triplet, J=4.2 Hz); 4.29 (2H, triplet, J=4.2 Hz); 7.10–7.40 (4H, multiplet). Mass spectrum (CI, m/z) : 212 ($M^+ + 1$), 176.

PREPARATION 2

3-(2-Fluorobenzyl)-5,6-dihydro-1,4,2-dioxazine

A procedure similar to that described in Preparation 1 was repeated, except that an equivalent amount of o-fluorophenylacetic acid was used in place of the o-chlorophenylacetic acid, to give the title compound as a colorless oil in a yield of 45%.

Mass spectrum (CI, m/z) : 196 ($M^+ + 1$), 109.

PREPARATION 3

3-(2,6-Difluorobenzyl)-5,6-dihydro-1,4,2-dioxazine

A procedure similar to that described in Preparation 1 was repeated, except that an equivalent amount of 2,6-difluorophenylacetic acid was used in place of the o-chlorophenylacetic acid, to give the title compound as a colorless oil in a yield of 45%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.61 (2H, singlet); 4.04 (2H, triplet, J=4.1 Hz); 4.30 (2H, triplet, J=4.1 Hz); 6.80–7.30 (4H, multiplet).

Mass spectrum (CI, m/z) : 214 ($M^+ + 1$), 127.

PREPARATION 4

2-Chlorobenzyl cyclopropyl ketone

10 ml of anhydrous diethyl ether were added to 0.45 g (18.5 mmole) of metallic magnesium, and then a solution of 2.0 ml (15.4 mmole) of 2-chlorobenzyl bromide in 10 ml of diethyl ether was slowly added dropwise to the resulting mixture, whilst stirring; the mixture was then stirred at room temperature for one hour. The resulting solution was slowly added dropwise to a solution of 1.1 ml of cyclopropyl cyanide in 10 ml of diethyl ether over a period of 30 minutes, and then the mixture was stirred at room temperature for 2 hours. At the end of this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture, and the mixture was stirred at room temperature for 15 minutes. 200 ml of ethyl acetate were then added to the reaction mixture, and the organic layer was separated, washed with water, with a saturated aqueous solution of sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous sodium sulfate; the solvent was then removed by distillation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 9:1 by volume mixture of toluene and ethyl acetate as the eluent, to give 2.0 g of the title compound as a colorless oil.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1}: 1695.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.86–0.92 (2H, multiplet); 1.06–1.12 (2H, multiplet); 1.96–2.02 (1H, multiplet); 3.98 (2H, singlet); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z) : 195 ($M^+ + 1$), 159.

PREPARATION 5

1-(2-Fluorophenyl)-2-pentanone

A procedure similar to that described in Preparation 4 was repeated, except that equivalent amounts of 2-fluorobenzyl bromide and butyl cyanide were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, to give the title compound as a colorless oil in a yield of 36%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.90 (3H, triplet, J=8.0 Hz); 1.52–1.73 (2H, multi-

plet); 2.45 (2H, triplet, J=8.0 Hz); 3.70 (2H, singlet); 7.00–7.30 (4H, multiplet).

Mass spectrum (CI, m/z) : 181 ($M^+ + 1$), 109.

PREPARATION 6

1-(2-Fluorophenyl)-2-hexanone

A procedure similar to that described in Preparation 4 was repeated, except that equivalent amounts of 2-fluorobenzyl bromide and pentyl cyanide were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, to give the title compound as a colorless oil in a yield of 46%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.90 (3H, triplet, J=8.0 Hz); 1.20–1.39 (2H, multiplet); 1.50–1.65 (2H, multiplet); 2.50 (2H, triplet, J=8.0 Hz); 3.70 (2H, singlet); 7.00–7.30 (4H, multiplet).

Mass spectrum (CI, m/z) : 195 ($M^+ + 1$), 109.

PREPARATION 7

1-(2-Fluorophenyl)-3,3-dimethyl-2-butanone

A procedure similar to that described in Preparation 4 was repeated, except that equivalent amounts of 2-fluorobenzyl bromide and t-butyl cyanide were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, to give the title compound as a colorless oil in a yield of 42%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.25 (9H, singlet); 3.80 (2H, singlet); 7.00–7.30 (4H, multiplet).

Mass spectrum (CI, m/z) : 195 ($M^+ + 1$), 109.

PREPARATION 8

Cyclopropyl 2-fluorobenzyl ketone

A procedure similar to that described in Preparation 4 was repeated, except that equivalent amounts of 2-fluorobenzyl bromide and cyclopropyl cyanide were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, to give the title compound as a colorless oil in a yield of 70%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.82–0.98 (2H, multiplet); 1.03–1.17 (2H, multiplet); 1.92–2.06 (1H, multiplet); 3.86 (2H, singlet); 7.10–7.30 (4H, multiplet).

Mass spectrum (CI, m/z) : 179 ($M^+ + 1$).

PREPARATION 9

1-(2-Fluorophenyl)-2-butanone

(a) 1-(2-Fluorophenyl)-2-nitro-1-butene 30 ml of acetic acid were added to 4.73 g (38.11 mmole) of 2-fluorobenzaldehyde, 4.41 g (49.49 mmole) of nitropropane and 3.23 g (41.90 mmole) of ammonium acetate, and the resulting mixture was heated under reflux, whilst stirring, for 4 hours. At the end of this time, the reaction mixture was cooled to room temperature, neutralized with an aqueous solution of sodium hydrogencarbonate and extracted with diethyl ether. The extract was dried over anhydrous magnesium sulfate, and then xylene was added to the solution. The mixture was concentrated by evaporation under reduced pressure, to give 7.4 g of the title compound as a pale yellow oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.25 (3H, triplet, J=6.5 Hz); 2.80 (2H, quartet, J=6.5 Hz); 7.00–7.60 (4H, multiplet); 8.03 (1H, singlet).

Mass spectrum (CI, m/z) : 196 ($M^+ + 1$), 149.

9(b) 1-(2-Fluorophenyl)-2-butanone

100 ml of 90% v/v aqueous acetic acid were added to 7.4 g of 1-(2-fluorophenyl)-2-nitro-1-butene [prepared as described in step (a) above], and then 12.11 g (190 mmole) of a zinc powder were added in portions to the resulting solution, whilst heating. The mixture was then heated under reflux, whilst stirring, for 4 hours. At the end of this time, the reaction mixture was left to stand overnight, and then the crystals which had precipitated were filtered off and washed with toluene. The filtrate was combined with the toluene washings, and the mixture was concentrated by evaporation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using toluene as the eluent, to give 1.85 g of the title compound as a pale brown oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.05 (3H, triplet, J=7.0 Hz); 2.53 (2H, quartet, J=7.0 Hz); 3.73 (2H, singlet); 7.00–7.40 (4H, multiplet).

Mass spectrum (CI, m/z) : 167 ($M^+ + 1$), 109.

PREPARATION 10

1-(2-Chlorophenyl)-2-propanone

Following a procedure similar to that described in Preparation 9, except that equivalent amounts of 2-chlorobenzaldehyde and nitroethane were used in place of the 2-fluorobenzaldehyde and nitropropane, the title compound was obtained as a brown oil in a yield of 27%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.20 (3H, singlet); 3.85 (2H, singlet); 7.15–7.45 (4H, multiplet).

Mass spectrum (CI, m/z) : 169 ($M^+ + 1$), 125.

PREPARATION 11

1-(2-chlorophenyl)-2-butanone

Following a procedure similar to that described in Preparation 9, except that an equivalent amount of 2-chlorobenzaldehyde was used in place of the 2-fluorobenzaldehyde, the title compound was obtained as a pale yellow oil in a yield of 17%.

Mass spectrum (CI, m/z) : 183 ($M^+ + 1$), 125.

PREPARATION 12

1-(2-Chlorophenyl)-2-heptanone

Following a procedure similar to that described in Preparation 9, except that equivalent amounts of 2-chlorobenzaldehyde and nitrohexane were used in place of the 2-fluorobenzaldehyde and nitropropane, the title compound was obtained as a pale yellow oil in a yield of 17%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.90 (3H, triplet, J=8.0 Hz); 1.20–1.40 (4H, multiplet); 1.50–1.70 (2H, multiplet); 2.50 (2H, triplet, J=10.0 Hz); 3.80 (2H, singlet); 7.20–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 225 ($M^+ + 1$), 125.

PREPARATION 13

Cyclobutyl 2-fluorobenzyl ketone

20 ml of anhydrous diethyl ether were added to 1.06 g (44 mmole) of metallic magnesium, and then a solution of 7.56 g (40 mmole) of 2-fluorobenzyl bromide in 10 ml of diethyl ether was slowly added dropwise to the resulting mixture, whilst stirring; the mixture was then stirred at room temperature for 1 hour. The resulting solution was slowly added dropwise to a solution of 4.74 g (40 mmole) of cyclobutanecarbonyl chloride in

30 ml of tetrahydrofuran, whilst cooling in a methanol-dry ice bath, over a period of 2 hours, and then the mixture was allowed to return to room temperature, whilst stirring, over a period of 2 hours. At the end of this time, 100 ml of water and 150 ml of diethyl ether were added to the reaction mixture, and the organic layer was separated, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 9:1 by volume mixture of toluene and hexane as the eluent, to give 2.97 g of the title compound as a pale yellow oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.65–2.40 (6H, multiplet); 3.31–3.48 (1H, multiplet); 3.67 (2H, singlet); 7.00–7 30 (4H, multiplet).

Mass spectrum (CI, m/z) : 193 ($M^+ + 1$), 137.

PREPARATION 14

5-Chloro-1-(2-chlorophenyl)-2-pentanone

Following a procedure similar to that described in Preparation 13, except that equivalent amounts of 2-chlorobenzyl bromide and 4-chlorobutyryl chloride were used in place of the 2 fluorobenzyl bromide and cyclobutanecarbonyl chloride, the title compound was obtained as a yellow oil in a yield of 79%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.96–2.15 (2H, multiplet); 2.69 (2H, triplet, J=7.7 Hz); 3.56 (2H, triplet, J=7.7 Hz); 3.86 (2H, singlet); 7.10–7.50 (4H, multiplet).

PREPARATION 15

1-(2-Chlorophenyl)-3,3,3-trifluoro-2-propanone

10 ml of anhydrous diethyl ether were added to 0.9 g (37.0 mmole) of metallic magnesium, and then a solution of 3.9 ml (30.8 mmole) of 2-chlorobenzyl chloride in 10 ml of diethyl ether was slowly added dropwise to the resulting mixture, with vigorous stirring, over a period of 30 minutes; the mixture was then stirred at room temperature for 1 hour. The resulting solution was slowly added dropwise to a solution of 4.3 ml (30.8 mmole) of trifluoroacetic anhydride in 40 ml of tetrahydrofuran, whilst cooling to about −70° C., and then the mixture was allowed to return to room temperature, whilst stirring, over a period of about 1 hour; after this, the mixture was left to stand overnight. At the end of this time, 200 ml of ethyl acetate were added to the resulting reaction mixture, and the organic layer was separated, washed with IN aqueous hydrochloric acid and with a saturated aqueous solution of sodium chloride, in that order, dried over anhydrous sodium sulfate and concentrated by evaporation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 10:2 by volume mixture of toluene and ethyl acetate as the eluent, to give 5.7 g of the title compound as a yellow oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.16 (2H, singlet); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z) : 223 ($M^+ + 1$), 125.

PREPARATION 16

2-Chloro-α-trifluoroacetylbenzyl bromide

2.0 g (9.0 mmole) of 1-(2-chlorophenyl)-3,3,3-trifluoro-2-propanone were dissolved in 30 ml of carbon tetrachloride, and then 0.46 ml (9.0 mmole) of bromine was added to the solution, which was then stirred at room temperature for 10 hours. At the end of this time, sodium hydrogensulfite was added to the reaction mixture, and the mixture was stirred at room temperature for 15 minutes, after which insolubles were removed by filtration. The filtrate was concentrated by evaporation under reduced pressure, and the residue was subjected to silica gel column chromatography, using a 10:2 by volume mixture of toluene and ethyl acetate as the eluent, to give 0.87 g of the title compound as a yellow oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 6.39 (1H, singlet); 7.30 7.70 (4H, multiplet).

Mass spectrum (CI, m/z) : 302 ($M^+ + 2$), 300 (M^+), 221.

PREPARATION 17

2-Chloro-α-(4-chlorobutyryl)benzyl bromide

Following a procedure similar to that described in Preparation 16, except that an equivalent amount of 1-(2-chlorophenyl)-5-chloro-2-pentanone was used in place of the 1-(2-chlorophenyl)-3,3,3-trifluoro-2-propanone, the title compound was obtained as a yellow oil in a yield of 72%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.01–2.14 (2H, multiplet); 2.40–2.90 (2H, multiplet); 3.49–3.61 (2H, multiplet); 5.98 (1H, singlet); 7.20–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 311 ($M^+ + 1$), 231.

PREPARATION 18

2-Chloro-α-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide

4.0 g (19 mmole) of 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine (prepared as described in Preparation 1) were dissolved in 40 ml of carbon tetrachloride, and then 4.1 g (23 mmole) of N-bromosuccinimide and 0.2 g of benzoyl peroxide were added to the solution, which was then stirred, whilst heating, for 8 hours. At the end of this time, 100 ml of ethyl acetate and 100 ml of hexane were added to the solution, and the mixture was stirred at room temperature for 30 minutes; insolubles were then removed by filtration. The filtrate was concentrated by evaporation under reduced pressure, to give 4.8 g of the title compound as a yellow oil.

Mass spectrum (CI, m/z) : 292 ($M^+ + 3$), 290 ($M^+ + 1$), 212.

PREPARATION 19

2-Fluoro-α-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide

Following a procedure similar to that described in Preparation 18, except that an equivalent amount of 3-(2-fluorobenzyl)-5,6-dihydro-1,4,2-dioxazine (prepared as described in Preparation 2) was used in place of the 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine, the title compound was obtained as a red oil in a yield of 98%.

Mass spectrum (CI, m/z) : 276 ($M^+ + 3$), 194.

PREPARATION 20

2,6-Difluoro-α-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide

Following a procedure similar to that described in Preparation 18, except that an equivalent amount of 3-(2,6-difluorobenzyl)-5,6-dihydro-1,4,2-dioxazine (prepared as described in Preparation 3) was used in place of the 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine, the title compound was obtained as a red oil in a yield of 57%.

Mass spectrum (CI, m/z) : 294 ($M^+ + 3$), 214.

PREPARATION 21

2-Chloro-α-cyclopropylcarbonylbenzyl bromide

Following a procedure similar to that described in Preparation 18, except that an equivalent amount of 2-chlorobenzyl cyclopropyl ketone (prepared as described in Preparation 4) was used in place of the 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine, the title compound was obtained as a red oil in a yield of 83%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.80–1.20 (4H, multiplet); 2.04–2.16 (1H, multiplet); 6.18 (1H, singlet); 7.20–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 275 ($M^+ + 3$), 193.

PREPARATION 22

2-Chlorobenzyl 4-fluorophenyl ketone

Following a procedure similar to that described in Preparation 13, except that equivalent amounts of 2-chlorobenzyl bromide and 4-fluorobenzoyl chloride were used in place of the 2-fluorobenzyl bromide and cyclobutanecarbonyl chloride, the title compound was obtained as a colorless powder in a yield of 34%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.40 (2H, singlet); 7.10–7.45 (6H, multiplet); 8.04–8.10 (2H, multiplet).

Mass spectrum (CI, m/z) : 249 ($M^+ + 1$), 213.

PREPARATION 23

2-Fluorobenzyl isopropyl ketone

Following a procedure similar to that described in Preparation 4, except that equivalent amounts of 2-fluorobenzyl chloride and isobutyronitrile were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, the title compound was obtained as a colorless oil in a yield of 25%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.15 (6H, doublet, J=7.5 Hz); 2.75 (1H, septet, J=7.5 Hz); 3.78 (2H, singlet); 6.97–7.30 (4H, multiplet).

Mass spectrum (CI, m/z) : 181 ($M^+ + 1$), 109.

PREPARATION 24

2-Nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride

24(a) 5-Acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

35.1 g (200 mmole) of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride and 38.57 g (200 mmole) of 28% w/v sodium methoxide in methanol were added to 200 ml of ethanol, and the resulting mixture was stirred at room temperature for 1 hour. The inorganic salt thus precipitated was filtered off, and the filtrate was concentrated to dryness by evaporation under reduced pressure. 50 ml of acetic anhydride were added all at once, whilst stirring, to the residue, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was then concentrated to dryness by evaporation under reduced pressure, and the residue thus obtained was subjected to silica gel column chromatography, using a 6:4 by volume mixture of toluene and ethyl acetate as the eluent, to give 29.32 g of the title compound as a yellow oil.

24(b) 5-Acetyl2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

20 ml of an acetic anhydride solution containing 5.43 g (30 mmole) of 5-acetyl-4,5,6,7-tetrahydrothieno.[3,2-c]pyridine [prepared as described in step (a) above] were added dropwise at 10° to 18° C. over a period of one hour to 30 ml of an acetic acid solution containing 4.2 g (60 mmole) of 90% fuming nitric acid, and the mixture was then stirred at a temperature not greater than 18° C. for 1 hour. The reaction mixture was then poured into ice-water and extracted with methylene chloride. The organic layer was separated, washed with a saturated aqueous solution of sodium hydrogencarbonate and with water, in that order, and dried over anhydrous magnesium sulfate. The solvent was then removed by distillation under reduced pressure, and the resulting residue was crystallized from a mixture of hexane and toluene, to give 4.46 g of the title compound as yellow crystals.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.19 & 2.21 (together 3H, each singlet); 2.82–3.05 (2H, multiplet); 3.80 & 3.95 (together 2H, each triplet, J=5.7 Hz); 4.55 & 4.66 (together 2H, each singlet); 7.66 (1H, singlet).

Mass spectrum (CI, m/z) : 227 ($M^+ + 1$).

24(c) 2-Nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride 2.38 g (10.53 mmole) of 5-acetyl-2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine [prepared as described in step (b) above] were heated under reflux for 2 hours in 60 ml of 10% w/v aqueous hydrochloric acid. The reaction mixture was then concentrated to dryness by evaporation under reduced pressure, to give 2.19 g of the title compound as brown crystals.

Nuclear Magnetic Resonance Spectrum (CD_3OD) δ ppm: 3.22 (2H, triplet, J=6.2 Hz); 3.60 (2H, triplet, J=6.2 Hz); 4.31 (2H, singlet); 7.87 (1H, singlet).

Mass spectrum (CI, m/z) : 185 ($M^+ + 1$).

PREPARATION 25

4,5,6,7-Tetrahydrofuro[3,2-c]pyridine

3.7 g (46 mmole) of a 37% aqueous formaldehyde solution were added dropwise at room temperature to 5.1 g (46 mmole) of 2-furylethylamine [the compound described, for example, in Brit., J. Pharmacol., 9, 376 (1954)], and the resulting mixture was stirred for about 15 minutes, after which it was extracted with diethyl ether. The organic extract was washed with water and dried over anhydrous sodium sulfate, and then the diethyl ether was removed by distillation under reduced pressure. 5 ml of dimethylformamide were added to the residue, and the resulting solution was added dropwise to 15 ml of dimethylformamide containing 3.6 g (100 mmole) of dry hydrogen chloride at room temperature. The resulting mixture was then stirred for 3 hours. At the end of this time, the greater part of the dimethylformamide was removed by distillation under reduced pressure, and then water and a 0.1N aqueous solution of sodium hydroxide were added to the residue so as to adjust its pH to a value of about 11; the mixture was then extracted with chloroform. The organic extract was washed with water and dried over anhydrous sodium sulfate. The chloroform was then removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a 50:1 by volume mixture of chloroform and methanol as the eluent, to give the title compound as a brown oil in a yield of 27%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.10–3.20 (4H, multiplet); 3.70–3.80 (2H, multiplet); 6.20 (1H, singlet); 7.27 (1H, singlet).

Mass spectrum (CI, m/z) : 124 ($M^+ + 1$).

PREPARATION 26

2-Fluorobenzyl 2-fluorocyclopropyl ketone

A procedure similar to that described in Preparation was repeated, except that an equivalent amount of 2-fluorocyclopropylcarbonyl chloride was used in place of the cyclobutylcarbonyl chloride, to give the title compound as a colorless oil in a yield of 27 %.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.38–1.58 (2H, multiplet); 2.34–2.56 (1H, multiplet); 3.90 (2H, singlet); 4.54–4.61 & 4.86–4.93 (together 1H, each multiplet); 7.05–7.35 (4H, multiplet).

Mass spectrum (CI, m/z) : 197 ($M^+ + 1$), 109.

PREPARATION 27

2-Fluoro-α-(2-fluorocyclopropylcarbonyl)benzyl bromide

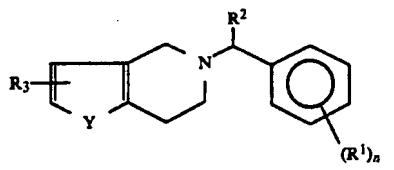
A procedure similar to that described in Preparation 18 was repeated, except that an equivalent amount of 2-fluorobenzyl 2-fluorocyclopropyl ketone was used in place of the 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine, to give the title compound as a colorless oil in a yield of 76 %.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.44–1.73 (2H, multiplet); 2.54–2.76 (1H, multiplet); 4.54–4.68 & 4.85–4.99 (together 1H, each multiplet); 5.93 (1H, singlet); 7.05–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 277 ($M^+ + 2$), 275 (M^+), 195.

We claim:

1. A compound of formula (I):



(I)

wherein

R^1 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halogen atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 1 to 10 carbon atoms; a substituted alkanoyl group which has from 2 to 10 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below; an alkenoyl group having from 3 to 6 carbon atoms; a substituted alkenoyl group which has from 3 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below; a cycloalkylcarbonyl group having from 4 to 8 carbon atoms; a substituted cycloalkylcarbonyl group which has from 4 to 8 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below; or a substituted benzoyl group having at least one substituent selected from the group consisting of substituents B, defined below;

R^3 represents a hydrogen atom; a hydroxy group; an alkoxy group having from 1 to 4 carbon atoms; a substituted alkoxy group which has from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents C, defined below; an aralkyloxy group in which the aralkyl part is as defined below; an alkanoyloxy group having from 1 to 18 carbon atoms; an alkenoyloxy group having from 3 to 6 carbon atoms; a cycloalkylcarbonyloxy group having from 4 to 8 carbon atoms; an arylcarbonyloxy group in which the aryl part is as defined below; an alkoxycarbonyloxy group having from 2 to 5 carbon atoms; an aralkyloxycarbonyloxy group in which the aralkyl part is as defined below; a phthalidyloxy group; a (5-methyl-2-oxo-1,3-dioxolen-4yl)methoxy group; a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group; a group of formula —N-R^aR^b: wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, alkyl groups having from 1 to 4 carbon atoms and substituted alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one substituent selected from the group consisting of substituents C, defined below; an aralkylamino group in which the aralkyl part is as defined below; an alkanoylamino group having from 1 to 18 carbon atoms; an alkenoylamino group having from 3 to 6 carbon atoms; a cycloalkylcarbonylamino group having from 4 to 8 carbon atoms: an arylcarbonylamino group in which the aryl part is as defined below; an alkoxycarbonylamino group having from 2 to 5 carbon atoms; an aralkyloxycarbonylamino group in which the aralkyl part is as defined below; a phthalidylamino group; a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylamino group; a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methylamino group, or a nitro group;

Y is a sulfur atom; and

n is an integer from 1 to 5, and, when n is an integer from 2 to 5, the groups represented by R^1 may be the same as or different from each other;

said substituents A are selected from the group consisting of halogen atoms, hydroxy groups, alkoxy groups having from 1 to 4 carbon atoms and cyano groups;

said substituents B are selected from the group consisting of alkyl groups having from 1 to 4 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms;

said substituents C are selected from the group consisting of alkoxy groups having from 1 to 4 carbon atoms, alkanoyloxy groups having from 1 to 6 carbon atoms and arylcarbonyloxy groups in which the aryl part is as defined below;

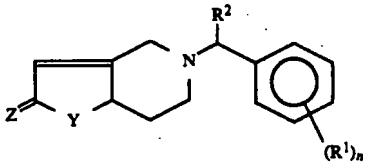
said aralkyl parts of said aralkyloxy, aralkyloxycarbonyloxy, aralkylamino and aralkyloxycarbonylamino groups are alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one aryl groups as defined below;

said aryl groups and said aryl parts of said arylcarbonyloxy groups and of said arylcarbonylamino groups having from 6 to 10 carbon atoms in a carbocyclic ring which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D, defined below; and

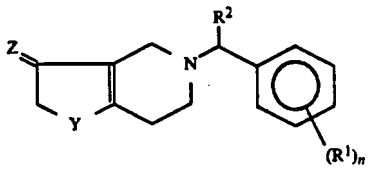
said substituents D are selected from the group consisting of the groups and atoms defined above in relation to R^1, other than said hydrogen atom;

or a tautomer thereof, or a pharmaceutically acceptable salt of said compound of formula (I) and of said tautomer.

2. The compound of claim 1, wherein said tautomer has the formula (Ia) or (Ib):



(Ia)



(Ib)

wherein R^1, R^2, Y and n are as defined above and Z represents group of formula =NH or an oxygen atom.

3. The compound of claim 1, wherein R^1 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group.

4. The compound of claim 1, wherein R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below of a substituted benzoyl group having at least one fluorine substituent; and

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups.

5. The compound of claim 1, wherein:

R^3 represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxy. carbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula $-NR^aR^b$ wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below; and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

6. The compound of claim 1, wherein:

R^1 represents a hydrogen atom, an alkyl group having from I to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an

alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below or a substituted benzoyl group having at least one fluorine substituent;

R^3 represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula $-NR^aR^b$ wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl groups and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below;

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups; and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

7. The compound of claim 6, wherein n is from 1 to 3.

8. The compound of claim 6, wherein n is 1.

9. The compound of claim 1, wherein R^1 represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group.

10. The compound of claim 1, wherein R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom.

11. The compound of claim 1, wherein R^3 represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, an amino group or a t-butoxycarbonylamino group.

12. The compound of claim 1, wherein:

R^1 represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R^3 represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)me-

thoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, an amino group or a t-butoxycarbonylamino group.

13. The compound of claim 12, wherein n is from 1 to 3.

14. The compound of claim 12, wherein n is 1.

15. The compound of claim 1, wherein R^1 represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group.

16. The compound of claim 1, wherein R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group.

17. The compound of claim 1, wherein:

R^1 represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group.

18. The compound of claim 17, wherein n is from 1 to 3.

19. The compound of claim 17, wherein n is 1.

20. The compound of claim 1, wherein R^2 represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom.

21. The compound of claim 1, wherein R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms.

22. The compound of claim 1, wherein:

R^1 represents a fluorine or chlorine atom;

R^2 represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom; and

R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms.

23. The compound of claim 22, wherein n is from 1 to 3.

24. The compound of claim 22, wherein n is 1.

25. The compound of claim 1, selected from the group consisting of 5-(2-fluoro-α-propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

26. The compound of claim 1, selected from the group consisting of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

27. The compound of claim 1, selected from the group consisting of 5-(2-chloro-α-cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

28. The compound of claim 1, selected from the group consisting of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

29. The compound of claim 1, selected from the group consisting of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

30. The compound of claim 1, selected from the group consisting of 2-butyryloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

31. The compound of claim 1, selected from the group consisting of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

32. The compound of claim 1, selected from the group consisting of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-valeryloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

33. The compound of claim 1, selected from the group consisting of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-hexanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

34. The compound of claim 1, selected from the group consisting of 2-t-butoxycarbonyloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

35. The compound of claim 1, selected from the group consisting of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

36. The compound of claim 1, selected from the group consisting of 5-(2-chloro-α-cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer and pharmaceutically acceptable salts thereof.

37. The compound of claim 1, selected from the group consisting of 5-(2-fluoro-α-propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer and pharmaceutically acceptable salts thereof.

38. The compound of claim 1, selected from the group consisting of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer and pharmaceutically acceptable salts thereof.

39. The compound of claim 1, selected from the group consisting of 2-acetoxy-5-(2-chloro-α-cyclo-

propylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

40. The compound of claim 1, selected from the group consisting of 5-[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer and pharmaceutically acceptable salts thereof.

41. The compound of claim 1, selected from the group consisting of 2-acetoxy-5-[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

42. A pharmaceutical composition for the treatment and prophylaxis of thrombosis o embolisms, comprising an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof, as claimed in claim 1.

43. The composition of claim 42, wherein:

R^1 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, or a substituted benzoyl group having at least one fluorine substituent, or a;

R^3 represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula $-NR^aR^b$ wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl groups and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below;

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups; and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

44. The composition of claim 42, wherein:

R^1 represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R^3 represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-

yl)methoxy group, an amino group or a t-butoxycarbonylamino group,

Y represents an oxygen or sulfur atom.

45. The composition of claim 42, wherein:

R^1 represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group;

46. The composition of claim 42, wherein:

R^1 represents a fluorine or chlorine atom;

R^2 represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom; and

R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms.

47. The composition of claim 42, wherein said blood platelet aggregation inhibitor is selected from the group consisting of:

5-(2-fluoro-α-propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(2-chloro-α-cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-butyryloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-valeryloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-hexanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-t-butoxycarbonyloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(2-chloro-α-cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

5-(2-fluoro-α-propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

2-acetoxy-5-(2-chloro-α-cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

2-acetoxy-5-[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

and pharmaceutically acceptable salts thereof.

48. A method for the treatment or prophylaxis of thrombosis or embolisms, comprising administering to a mammal an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof, as claimed in claim 1.

49. The method of claim 48, wherein:

R^1 represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, of a substituted benzoyl group having at least one fluorine substituent;

R^3 represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonyloxy group having from 2

to 5 carbon atoms, a benzyloxycarbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula —NR^aR^b wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl groups and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below;

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups; and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

50. The method of claim 48, wherein:

R^1 represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R^3 represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, an amino group or a t-butoxycarbonylamino group.

51. The method of claim 48, wherein:

R^1 represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group;

R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group.

52. The method of claim 48, wherein:

R^1 represents a fluorine or chlorine atom;

R^2 represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom;

R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms; and

Y represents a sulfur atom.

53. The method of claim 48, wherein said blood platelet aggregation inhibitor is selected from the group consisting of:

5-(2-fluoro-α-propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(2-chloro-α-cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-butyryloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-valeryloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-hexanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-t-butoxycarbonyloxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(2-chloro-α-cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

5-(2-fluoro-α-propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

2-acetoxy -5-(2-chloro-α-cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

2-acetoxy-5-[α-(2-fluorocyclopropylcarbonyl-2-fluorobenzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

and pharmaceutically acceptable salts thereof.

54. The compound of claim **1**, wherein R^1 represents a fluorine atom.

55. The compound of claim **1**, wherein R^1 represents a chlorine atom.

56. The compound of claim **1**, wherein

R^1 represents a fluorine atom;

R^2 represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom;

R^3 represents a hydrogen atom, a hydroxy group, a privaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms; and

Y represents a sulfur atom.

* * * * *

EXHIBIT 5
CERTIFICATE OF CORRECTION
FOR USP 5,288,726

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,288,726
DATED : February 22, 1994
INVENTOR(S) : Koike et al

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 68, line 1: delete "of" and insert --, or--.

Column 69, line 15: after "below" insert -- , --.

Column 75, lines 2 and 3: after "group" delete ", Y represents an oxygen or sulfur atom".

Column 75, line 23: delete ";" and insert -- . --.

Column 76, line 51, after "below," delete "of" and insert --or--.

Column 78, line 32, after ";" insert --and--.

Column 78, lines 36-38, delete "; and Y represents a sulfur atom".

Signed and Sealed this

Twenty-first Day of April, 1998

Bruce Lehman

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

EXHIBITS 6A, 6B and 6C
MAINTENANCE FEE PAYMENT RECEIPTS
FOR USP 5,288,726

UNITED STATES PATENT AND TRADEMARK OFFICE

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FRISHAUF, HOLTZ, GOODMAN & CHICK, PC
220 Fifth Avenue
16TH Floor
NEW YORK NY 10001-7708

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,288,726	**$1,020.00**	**$0.00**	**04/24/97**	**07/941,676**	**02/22/94**	**09/08/92**	**04**	**NO**	**920676/HG**

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,288,726	**$1,950.00**	**$0.00**	**04/23/01**	**07/941,676**	**02/22/94**	**09/08/92**	**08**	**NO**	**920676/HG**

UNITED STATES PATENT AND TRADEMARK OFFICE

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MAINTENANCE FEE STATEMENT

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The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,288,726	**$3,800.00**	**$0.00**	**03/04/05**	**07/941,676**	**02/22/94**	**09/08/92**	**12**	**NO**	**920676/HG**

EXHIBIT 7
IND LOG

Registration Number 63,449
Roadmap Information

Sponsor's Serial Number	Sponsor's Submission Date	Description of Submission	CD Serial Number	Paper Only	File or Folder Name
0574		New Investigators H7T-MC-TABY-TACW	N/A	X	N/A
0573	15-JUL-2009	Seq#0573: Toxicology Report CCGS03 Amendment 02	N/A	X	N/A
0572	02-JUL-2009	Seq#0572: Prasugrel DNA Banking FDA Reg Response	N/A	X	N/A
0571	02-JUL-2009	Seq#0571:medwatch	N/A	X	N/A
0570	26-JUN-2009	Seq#0570: Initial Protocol, Protocol Amendment(a), Amendment Summary(a), Addendum(1), Investigator, CRO Information H7T-MC-TACW	N/A	X	N/A
0569	25-JUN-2009	Seq#0569: New Investigators H7T-MC-TABY	N/A	X	N/A
0568	28-MAY-2009	Seq#0568: Medwatch	N/A	X	N/A
0567	19-MAY-2009	Seq#0567: Medwatch	N/A	X	N/A
0566	22-MAY-2009	Seq#0566: Granular Clinical Study Report H7T-EW-TADB: 03 CSR Synopsis, 04 CSR Body, 06 CSR Sample CRFs, 07 CSR ERB ICD, 08 CSR Inv Info, 09 CSR Inv Sig, 11 CSR Randomisation, 12 CSR Audit Info, 17 CSR Discont Patients, 20 CSR Demographics, 23 CSR AE Listings	N/A	X	N/A
0565	23-JUN-2009	Seq#0565: Administrative Corrections of Indication Change on eCTD Backbone for H7T-MC-TABY From PCI to ACS-MM	N/A	X	N/A
0564	07-MAY-2009	Seq#0564: Briefing Document, Protocol Amendment/Summary H7T-MC-TABY(b)	N/A	X	N/A
0563	14-APR-2009	Seq#0563: Regulatory Response to FDA Request April 1, 2009 PKPD TADA and TADC Questions	N/A	X	N/A
0562	07-APR-2009	H7T-MC-TADR 03 Synopsis, 04 Synopsis Body, 06 Synopsis Sample CRFs, 09 Synopsis Inv Sig, 25 Synopsis Case Report Forms	N/A	X	N/A
0561	26-MAR-2009	Seq#0561: H7T-MC-TACL Clinical Study Synopsis 6-Month Update	N/A	X	N/A
0560	27-MAR-2009	Seq#0560: Response TRILOGY Questions	N/A	X	N/A
0559	13-APR-2009	New Investigators H7T-MC-TABY	N/A	X	N/A
0558	01-APR-2009	Seq#0558: Investigator's Brochure NI1129	N/A	X	N/A
0557	10-MAR-2009	Seq#0557: Response to FDA Letter Dated 19 September 2008 Concerning Study H7T-MC-TABY(TRILOGY)	N/A	X	N/A
0556	15-MAY-2009	Seq#0556: New Investigators H7T-MC-TABY	N/A	X	N/A
0555	23-FEB-2009	CMC Amendment Roller Compaction 3 Process	N/A	X	N/A
0554	13-MAR-2009	Seq#0554: New Investigators H7T-MC-TABY, H7T-EW-TADA-TADC	N/A	X	N/A
0553	06-FEB-2009	Regulatory Response: Nonclinical Pharmacology Report CCGS03	N/A	X	N/A

0552	27-JAN-2009	Toxicology Vivo Reports: CCGS02, CCGS03, LYP4	N/A	X	N/A
0551	13-FEB-2009	New Investigators H7T-MC-TABY	N/A	X	N/A
0550	20-JAN-2009	New Protocols, Investigator, and CRO Information H7T-EW-TADA-TADC	N/A	X	N/A
0549	19-JAN-2009	New Investigators H7T-MC-TABY	N/A	X	N/A
0548		Annual Report	N/A	X	N/A
0547	16-DEC-2008	New Investigators H7T-MC-TABY	N/A	X	N/A
0546	04-DEC-2008	Medwatch	N/A	X	N/A
0545	21-NOV-2008	Response to FDA Request Protocol in vivo Studies	N/A	X	N/A
0544	21-NOV-2008	New Investigators H7T-MC-TABY-TADR	N/A	X	N/A
0543	10-NOV-2008	New Investigators H7T-MC-TABY	N/A	X	N/A
0542	07-NOV-2008	Response to IR Letter Dated October 17, 2008 Metabolites Cell Culture Xenograft	N/A	X	N/A
0541	27-OCT-2008	Initial Protocol H7T-MC-TADR, CRO Information, and CMC Note to Reviewer	N/A	X	N/A
0540	17-OCT-2008	New Investigators H7T-MC-TABY	N/A	X	N/A
0539	16-OCT-2008	Clinical Study Report H7T-MC-TACT: 03 Synopsis, 04 Body, 05 Protocol Cover, 06 Sample CRFs, 07 ERB ICD, 08 Investigator Information, 09 Investigator Signature, 10 List Patients, 11 Randomisation, 12 Audit Information, Demographic Data, AE Listings, Protocol, Synopsis	N/A	X	N/A
0538	16-SEP-2008	New Investigator and CRO Information H7T-EW-TADB	N/A	X	N/A
0537	04-SEP-2008	Initial Protocol, Protocol Amendment/Summary H7T-EW-TADB	N/A	X	N/A
0536	03-SEP-2008	September 2008 CMC Amendment	N/A	X	N/A
0535	22-AUG-2008	New investigators H7T-MC-TABY	N/A	X	N/A
0534	25-JUL-2008	Clinical Study Report H7T-MC-TABN	N/A	X	N/A
0533	18-JUL-2008	ADME Report 2007IV-PG002, New Investigators H7T-MC-TACA-TABM	N/A	X	N/A
0532	03-JUL-2008	Clinical Study Synopsis and Statistical Analysis Plan for study H7T-MC-TACL: TRITON TIMI Registry	N/A	X	N/A
0531	27-JUN-2008	New Investigators H7T-MC-TABY	N/A	X	N/A
0530	20-JUN-2008	Requested Information Concerning Study H7T-MC-TABY(a) (TRILOGY ACS) Malignancy eCRFs	N/A	X	N/A
0529	20-JUN-2008	Initial Protocol H7T-MC-TABY(a), Investigator, and CRO Information (Note: amendment(a) is being submitted as the initial protocol)	N/A	X	N/A
0528	09-MAY-	CM&C Amendment May 2008	N/A	X	N/A

	2008				
0527	07-MAY-2008	Correspondence: Request for Comment on Proposal to Begin Study H7T-MC-TABY(TRILOGY)	N/A	X	N/A
0526	06-MAY-2008	Investigators H7T-MC-TAAL-TABM-TACA CRO-TABM-TACA	N/A	X	N/A
0525	08-APR-2008	Clinical Pharm Synopsis H7T-FW-TABX(a)	N/A	X	N/A
0524	15-APR-2008	Clinical Study Synopsis H7T-EW-TACT	N/A	X	N/A
0523	26-MAR-2008	Initial Protocol, Investigator, and CRO Information H7T-MC-TACA	N/A	X	N/A
0522	19-MAR-2008	Withdrawal of Consent TRITON TIMI-38	N/A	X	N/A
0521	19-MAR-2008	Clinical Study Synopsis H7T-MC-TACL: TRITON TIMI Registry	N/A	X	N/A
0520	13-MAR-2008	Slides for March 17, 2008 Teleconference	N/A	X	N/A
0519	03-MAR-2008	Clinical Study Report H7T-EW-TACS	N/A	X	N/A
0518	03-MAR-2008	Clinical Study Report H7T-EW-TACR	N/A	X	N/A
0517	11-FEB-2008	Investigator's Brochure NI1129	N/A	X	N/A
0516	14-JAN-2008	Annual Report	N/A	X	N/A
0515	16-JAN-2008	Special Protocol Assessment Briefing Document with Draft Protocol Amendment/Summary H7T-MC-TABY(a)	N/A	X	N/A
0514	16-JAN-2008	Investigators H7T-MC-TAAL	N/A	X	N/A
0513	18-DEC-2007	Protocol Amendment/Summary H7T-MC-TABM(b)	N/A	X	N/A
0512	17-DEC-2007	Clinical Study Report H7T-EW-TAAT	N/A	X	N/A
0511	13-DEC-2007	Request for Pre-Filing Meeting	N/A	X	N/A
0510	06-DEC-2007	Clincial Study Synopsis H7T-MC-TABN-TABM	N/A	X	N/A
0509	04-DEC-2007	Toxicology Reports APS-153-145, K23-0002, K23-0003 Mouse Fibroblast Cell Line	N/A	X	N/A
0508	29-NOV-2007	Clinical Study Report H7T-EW-TACK	N/A	X	N/A
0507	29-NOV-2007	Clinical Study Report H7T-EW-TABW	N/A	X	N/A
0506	27-NOV-2007	Investigators H7T-MC-TAAL	N/A	X	N/A
0505	14-NOV-2007	Clinical Study Report H7T-EW-TAAS	N/A	X	N/A
0504	14-NOV-2007	Pharmacogenomics Data Submission: Summary of FDA Meetings and Agreements	N/A	X	N/A
0503	08-NOV-2007	November 3, 2007 Teleconference Minutes Japanese Datasets	N/A	X	N/A
0502	31-OCT-2007	Clinical Study Report H7T-EW-TACJ	N/A	X	N/A

0501	31-OCT-2007	Nonclinical Pharmacology Report AMS22	N/A	X	N/A
0500	31-OCT-2007	Clinical Study Report H7T-MC-TABR	N/A	X	N/A
0499	25-OCT-2007	Initial Protocol, Investigator, and CRO Information H7T-EW-TACT	N/A	X	N/A
0498	23-OCT-2007	Information Amendment: Preliminary Safety Analysis of Study H7T-MC-TAAL, TRITON-TIMI 38	N/A	X	N/A
0497	19-OCT-2007	Blinded Medwatch	N/A	X	N/A
0496	12-OCT-2007	Final Clinical Study Report H7T-MC-TABL	N/A	X	N/A
0495	03-OCT-2007	Investigators H7T-MC-TAAL, H7T-FW-TABX	N/A	X	N/A
0494	03-OCT-2007	Clinical Study Report H7T-FW-TACF	N/A	X	N/A
0493	03-OCT-2007	Clinical Study Report H7T-EW-TACG	N/A	X	N/A
0492	03-OCT-2007	Final Clinical Study Report H7T-EW-TABZ and CRO Information	N/A	X	N/A
0491	03-OCT-2007	Final Clinical Study Report H7T-EW-TAAX and CRO Information	N/A	X	N/A
0490	03-OCT-2007	Final Clinical Study Report H7T-EW-TAAW	N/A	X	N/A
0489	02-OCT-2007	Correspondence Request for Response: Acceptability of Study Synopses for Phase 1 and 2 non-IND studies Conducted in Japan	N/A	X	N/A
0488	02-OCT-2007	Blinded Medwatch	N/A	X	N/A
0487	27-SEP-2007	Final Clinical Study Report H7T-EW-TAAV	N/A	X	N/A
0486	27-SEP-2007	Final Clinical Study Report H7T-EW-TAAU	N/A	X	N/A
0485	27-SEP-2007	Final Clinical Study Report H7T-EW-TABF	N/A	X	N/A
0484	27-SEP-2007	Final Clinical Study Report H7T-EW-TAAR	N/A	X	N/A
0483	21-SEP-2007	Blinded Medwatch	N/A	X	N/A
0482	18-SEP-2007	TAAL Amendment/Summary Statistical Analysis Plan for Intregrated Safety	N/A	X	N/A
0481	18-SEP-2007	TABR Statistical Analysis Plan for Genomics	N/A	X	N/A
0480	18-SEP-2007	Statistical Analysis Plan Amendment/Summary H7T-MC-TAAL(b) Percutaneous Coronary Intervention	N/A	X	N/A
0479	18-SEP-2007	Blinded Medwatch	N/A	X	N/A
0478	13-SEP-2007	Special Protocol Assessment H7T-MC-TABY and CEC Charter	N/A	X	N/A
0477	19-OCT-2007	Blinded Medwatch	N/A	X	N/A
0476	30-AUG-2007	Statistical Analysis Plan Stage 3 Amendment and Summary H7T-MC-TAAL(a)	N/A	X	N/A
0475	28-AUG-	Protocol Amendment/Summary and Investigators H7T-EW-	N/A	X	N/A

	2007	TACR(a)			
0474	28-AUG-2007	Final Clinical Study Report H7T-EW-TAAZ	N/A	X	N/A
0473	23-AUG-2007	Blinded Medwatch	N/A	X	N/A
0472	21-AUG-2007	Blinded Medwatch	N/A	X	N/A
0471	20-AUG-2007	Investigators H7T-MC-TAAL	N/A	X	N/A
0470	20-AUG-2007	Initial Protocol H7T-EW-TACR and CRO and H7T-EW-TACS and CRO (no investigator docs at this time)	N/A	X	N/A
0469	07-AUG-2007	Blinded Medwatch	N/A	X	N/A
0468	01-AUG-2007	Correspondence: Statistical Analysis Plan for Study H7T-MC-TABL	N/A	X	N/A
0467	30-JUL-2007	Blinded Medwatch	N/A	X	N/A
0466	24-JUL-2007	Request for TRADEMARK Review: FDA Response Requested	N/A	X	N/A
0465	18-JUL-2007	Blinded Medwatch	N/A	X	N/A
0464	16-JUL-2007	Investigators H7T-MC-TAAL, H7T-MC-TABL	N/A	X	N/A
0463	13-JUL-2007	Medwatch JP2007060005316 F #2 - not blinded	N/A	X	N/A
0462	10-JUL-2007	Protocol Amendment H7T-MC-TABN(b) and Protocol Amendment Summary H7T-MC-TABN(b)	N/A	X	N/A
0461	05-JUL-2007	Correspondence Pre-NDA Mtg. Follow-up	N/A	X	N/A
0460	05-JUL-2007	Medwatch JP200706005316 F	N/A	X	N/A
0459	28-JUN-2007	Medwatch JP200706005316 Initial	N/A	X	N/A
0458	26-JUN-2007	Clinical Endpoint Comittee Charter (CEC - R4) for H7T-MC-TAAL	N/A	X	N/A
0457	19-JUN-2007	Blinded Medwatch	N/A	X	N/A
0456	15-JUN-2007	Investigators H7T-MC-TABM	N/A	X	N/A
0455	13-JUN-2007	Briefing Document for H7T-MC-TABY Type C Meeting on July 13, 2007	N/A	X	N/A
0454	12-JUN-2007	Blinded Medwatch	N/A	X	N/A
0453	11-JUN-2007	General Correspondence: Early PopPK Lock Plan for H7T-MC-TAAL	N/A	X	N/A
0452	11-JUN-2007	Correspondence: PopPKPD Satatistical Analysis Plan for H7T-MC-TAAL	N/A	X	N/A
0451	08-JUN-2007	Correspondence: May 30, 2007 Pre-NDA Sponsor Meeting Minutes	N/A	X	N/A
0450	30-MAY-2007	Blinded Medwatches	N/A	X	N/A
0449	25-MAY-2007	Clinical Study Report H7T-MC-TABR	N/A	X	N/A

0448	22-MAY-2007	Protocol Amendment H7T-EW-TACJ(b) and Amendment Summary H7T-EW-TACJ(b)	N/A	X	N/A
0447	22-MAY-2007	Clinical Study Report H7T-EW-TABV	N/A	X	N/A
0446	22-MAY-2007	Clinical Study Report H7T-EW-TABS	N/A	X	N/A
0445	22-MAY-2007	blinded medwatch	N/A	X	N/A
0444	21-MAY-2007	Correspondence: Response to FDA Comments on Japanese Clinical Pharmacology Study Proposal Submitted	N/A	X	N/A
0443	17-MAY-2007	Statistical Analysis Plan for H7T-MC-TAAL	N/A	X	N/A
0442	17-MAY-2007	Blinded medwatch	N/A	X	N/A
0441	15-MAY-2007	Investigators for H7T-EW-TACG, H7T-MC-TAAL	N/A	X	N/A
0440	15-MAY-2007	Toxicology Report 1982.6263	N/A	X	N/A
0439	08-MAY-2007	Blinded Medwatch	N/A	X	N/A
0438	07-MAY-2007	General Correspondence: Sponsor Meeting Minutes from April 25, 2007 Teleconference	N/A	X	N/A
0437	01-MAY-2007	General Correspondence: Communication of DMC recommendation for H7T-MC-TABL	N/A	X	N/A
0436	30-APR-2007	Briefing Document for PreNDA Meeting on May 30, 2007	N/A	X	N/A
0435	19-APR-2007	Investigators H7T-MC-TABN	N/A	X	N/A
0434	17-APR-2007	Request to Regulator: Request to Cross-Reference IND Annual Report	N/A	X	N/A
0433	16-APR-2007	Request to Regulator: Type C Meeting Request (Follow-up to June 20, 2006 Type B meeting) to discuss the design of TABY protocol	N/A	X	N/A
0432	16-APR-2007	CEC Charter for H7T-MC-TABL and Stent Thrombosis Adjudication CRF for H7T-MC-TABL	N/A	X	N/A
0431	16-APR-2007	CEC Charter (Revision 3) for H7T-MC-TAAL and CEC Adjudication: Stent Thrombosis CRF for H7T-MC-TAAL	N/A	X	N/A
0430	13-APR-2007	Protocol Amendment H7T-EW-TABW(c) and Amendment Summary H7T-EW-TABW(c)	N/A	X	N/A
0429	13-APR-2007	Protocol Amendment H7T-EW-TACJ(a) and Amendment Summary H7T-EW-TACJ(a)	N/A	X	N/A
0428	10-APR-2007	Blinded Medwatch	N/A	X	N/A
0427	30-MAR-2007	Blinded Medwatch	N/A	X	N/A
0426	29-MAR-2007	Response to FDA Request for the Population PK/PD Analysis Plan for Study H7T-EW-TACJ	N/A	X	N/A
0425	28-MAR-2007	Request to Regulator: Request for a Type C Teleconference to clarify comments received via email on March 22, 2007 from Dr. Karen Hicks of FDA	N/A	X	N/A
0424	27-MAR-2007	Blinded Medwatch	N/A	X	N/A
0423	26-MAR-2007	Correspondence: Request for FDA Response, Acceptability of Study Synopses for Phase 1 and 2 non-IND studies conducted in	N/A	X	N/A

		Japan			
0422	20-MAR-2007	Blinded Medwatch	N/A	X	N/A
0421	19-MAR-2007	Clinical Study Report H7T-FW-TAAQ	N/A	X	N/A
0420	19-MAR-2007	Clinical Study Report H7T-EW-TAAO	N/A	X	N/A
0419	19-MAR-2007	Clinical Study Report H7T-EW-TAAN	N/A	X	N/A
0418	19-MAR-2007	Investigators H7T-MC-TAAL, H7T-MC-TABN, H7T-MC-TABL	N/A	X	N/A
0417	13-MAR-2007	Blinded Medwatch	N/A	X	N/A
0416	08-MAR-2007	Meeting Minutes 27 Feb 2007 - also submitted were TIMI slides and TIMI registry	N/A	X	N/A
0415	06-MAR-2007	Request to Regulator: Type B Meeting Request, Pre-NDA Meeting	N/A	X	N/A
0414	02-MAR-2007	CMC Amendment supporting TACK protocol	N/A	X	N/A
0413	02-MAR-2007	Blinded Medwatch	N/A	X	N/A
0412	28-FEB-2007	Initial Protocol H7T-EW-TACK, CRO, and investigator	N/A	X	N/A
0411	27-FEB-2007	Blinded Medwatch	N/A	X	N/A
0410	22-FEB-2007	Blinded Medwatch	N/A	X	N/A
0409	16-FEB-2007	Blinded Medwatch	N/A	X	N/A
0408	16-FEB-2007	Investigators H7T-MC-TAAL, H7T-MC-TABL	N/A	X	N/A
0407	08-FEB-2007	Request for TRADEMARK Review: FDA response Requested	N/A	X	N/A
0406	05-FEB-2007	Blinded Medwatch - Response to FDA Request for Information	N/A	X	N/A
0405	31-JAN-2007	Protocol Amendment H7T-MC-TABM(a), Protocol Amendment Summary H7T-MC-TABM(a), Protocol Sample Banking Addendum H7T-MC-TABM(a)(1.1) and Protocol Sample Storage Addendum H7T-MC-TABM(a)(2.1)	N/A	X	N/A
0404	25-JAN-2007	Blinded Medwatch	N/A	X	N/A
0403	23-JAN-2007	Investigator's Brochure NI1129, Approved 16 Jan 2007	N/A	X	N/A
0402	19-JAN-2007	Toxicology Report No. APS-151-172, APS-151-172 Amendment 1, APS-151-172 Amendment 2	N/A	X	N/A
0401	19-JAN-2007	Toxicology Report No. APS-151-171, APS-151-171 Amendment 1, APS-151-171 Amendment 2	N/A	X	N/A
0400	19-JAN-2007	Toxicology Report No. APS-151-155, and Amendment 01 to APS-151-155	N/A	X	N/A
0399	18-JAN-2007	ADME Report No. ATS-151-091, ATS-151-092, ATS-151-093, ATR-151-053, APS-151-130, APS-151-132, APS-151-138, APS-151-125	N/A	X	N/A
0398	17-JAN-2007	Blinded medwatch	N/A	X	N/A

0397	12-JAN-2007	Blinded Medwatch	N/A	X	N/A
0396	20-DEC-2006	Annual Report	N/A	X	N/A
0395	22-DEC-2006	Blinded Medwatch	N/A	X	N/A
0394	21-DEC-2006	Blinded Medwatches	N/A	X	N/A
0393	19-DEC-2006	Blinded Medwatches	N/A	X	N/A
0392	15-DEC-2006	Investigators H7T-MC-TABL, H7T-MC-TABM, H7T-MC-TAAL	N/A	X	N/A
0391	12-DEC-2006	Blinded Medwatch	N/A	X	N/A
0390	12-DEC-2006	Protocol Amendment H7T-MC-TABN(a) and Protocol Amendment Summary H7T-MC-TABN(a) (no investigator)	N/A	X	N/A
0389	06-DEC-2006	Initial Protocol H7T-FW-TABX, Protocol Amendment H7T-FW-TABX(a) and Protocol Amendment Summary H7T-FW-TABX(a) and investigator and CRO. Patients will be enrolled under amendment TABX(a)	N/A	X	N/A
0388	05-DEC-2006	Response to FDA Request for information: Angiograms for Medwatch case EWC050644469 (on CD)	N/A	X	N/A
0387	05-DEC-2006	Response to FDA Request for Information - Summary Reports of Stent Thrombosis	N/A	X	N/A
0386	05-DEC-2006	Blinded Medwatch	N/A	X	N/A
0385	05-DEC-2006	Initial Protocol H7T-EW-TACG and investigator and CRO	N/A	X	N/A
0384	05-DEC-2006	Initial Protocol H7T-EW-TACJ and investigator and CRO	N/A	X	N/A
0383	30-NOV-2006	Correspondence: Communication of DMC Recommendation at Interim Analysis 3 for H7T-MC-TAAL	N/A	X	N/A
0382	30-NOV-2006	Response to FDA Request for Information regarding case EWC050644469 and HU200605003292 (Case Report Forms)	N/A	X	N/A
0381	28-NOV-2006	Blinded Medwatch	N/A	X	N/A
0380	22-NOV-2006	Blinded Medwatch Reports	N/A	X	N/A
0379	22-NOV-2006	Correspondence: Request for comment on Lilly's Response to FDA's Request for Information	N/A	X	N/A
0378	21-NOV-2006	Request for Confirmation of Statistical Significance Required for Study H7T-MC-TABY	N/A	X	N/A
0377	20-NOV-2006	blinded medwatch	N/A	X	N/A
0376	17-NOV-2006	Investigators H7T-MC-TAAL, H7T-MC-TABL	N/A	X	N/A
0375	16-NOV-2006	Blinded Medwatch	N/A	X	N/A
0374	15-NOV-2006	Blinded Medwatch	N/A	X	N/A
0373	10-NOV-2006	Blinded Medwatch	N/A	X	N/A

0372	08-NOV-2006	Correspondence: DMC Request Letter	N/A	X	N/A
0371	07-NOV-2006	CMC Type C Briefing Document for November 20, 2006 FDA Meeting	N/A	X	N/A
0370	03-NOV-2006	Blinded Medwatch	N/A	X	N/A
0369	31-OCT-2006	Type C Meeting Request (CMC)	N/A	X	N/A
0368	31-OCT-2006	Blinded Medwatch	N/A	X	N/A
0367	26-OCT-2006	Blinded Medwatch	N/A	X	N/A
0366	24-OCT-2006	Change in CRO obligations for study H7T-FW-TACF	N/A	X	N/A
0365	24-OCT-2006	Investigators H7T-MC-TAAL, H7T-EW-TABW, H7T-MC-TABL	N/A	X	N/A
0364	23-OCT-2006	Correspondence: Lilly Meeting Minutes from the Sept 22, 2006 FDA Meeting Concerning Study H7T-MC-TABY	N/A	X	N/A
0363	19-OCT-2006	Blinded Medwatch	N/A	X	N/A
0362	18-OCT-2006	Sample Case Report Forms H7T-MC-TAAL(Non Office Visit, CEC Adjudication updates, GP Antagonist Substudy addenda 11)	N/A	X	N/A
0361	17-OCT-2006	Blinded Medwatch Reports	N/A	X	N/A
0360	16-OCT-2006	CM&C Amendment 2006	N/A	X	N/A
0359	10-OCT-2006	Blinded Medwatch	N/A	X	N/A
0358	04-OCT-2006	Safety Monitoring Plan for H7T-MC-TABL and Clinical Endpoint Committee (CEC) Charter for H7T-MC-TABL	N/A	X	N/A
0357	03-OCT-2006	Blinded Medwatch	N/A	X	N/A
0356	28-SEP-2006	Blinded Medwatch	N/A	X	N/A
0355	26-SEP-2006	Protocol Addendum H7T-MC-TABR(1) Sample Banking Addendum	N/A	X	N/A
0354	26-SEP-2006	Blinded Medwatch	N/A	X	N/A
0353	22-SEP-2006	Communication of DMC Recommendation at Interim Analysis 2 for H7T-MC-TAAL	N/A	X	N/A
0352	21-SEP-2006	Blinded Medwatch	N/A	X	N/A
0351	19-SEP-2006	Investigators H7T-MC-TAAL, H7T-MC-TABM	N/A	X	N/A
0350	19-SEP-2006	Blinded Medwatch	N/A	X	N/A
0349	12-SEP-2006	Blinded Medwatch	N/A	X	N/A
0348	07-SEP-2006	blinded Medwatch	N/A	X	N/A
0347	07-SEP-2006	Protocol Addendum H7T-MC-TAAL (HDL Substudy) done independently by an investigator	N/A	X	N/A
0346	01-SEP-	Blinded Medwatch	N/A	X	N/A

	2006				
0345	31-AUG-2006	Blinded Medwatch	N/A	X	N/A
0344	30-AUG-2006	Correspondence: Stopping of protocol Addendum H7T-MC-TAAL(10)	N/A	X	N/A
0343	30-AUG-2006	Updated Data Monitoring Committee Charter (DMC), Revision 4, for H7T-MC-TAAL	N/A	X	N/A
0342	29-AUG-2006	Blinded Medwatch	N/A	X	N/A
0341	28-AUG-2006	Type B Briefing Document for September 22, 2006 Meeting - H7T-MC-TABY ACS Medical Management Meeting #2	N/A	X	N/A
0340	22-AUG-2006	Blinded Medwatch	N/A	X	N/A
0339	18-AUG-2006	Investigators H7T-MC-TAAL, H7T-MC-TABM, H7T-EW-TABW	N/A	X	N/A
0338	16-AUG-2006	Blinded Medwatch	N/A	X	N/A
0337	15-AUG-2006	Blinded Medwatch Reports	N/A	X	N/A
0336	08-AUG-2006	Blinded Medwatch	N/A	X	N/A
0335	07-AUG-2006	Protocol H7T-FW-TACF and investigator	N/A	X	N/A
0334	07-AUG-2006	Investigator for H7T-EW-TABV	N/A	X	N/A
0333	03-AUG-2006	Investigator and CRO for H7T-MC-TABL	N/A	X	N/A
0332	02-AUG-2006	Blinded Medwatch	N/A	X	N/A
0331	02-AUG-2006	Initial Protocol H7T-EW-TABZ and investigator	N/A	X	N/A
0330	01-AUG-2006	Blinded Medwatch	N/A	X	N/A
0329	27-JUL-2006	Blinded Medwatch	N/A	X	N/A
0328	27-JUL-2006	Correspondence: Termination of Study H7T-EW-TABV	N/A	X	N/A
0327	27-JUL-2006	Protocol Amendment H7T-EW-TABW(b) and amendment summary H7T-EW-TABW(b)	N/A	X	N/A
0326	24-JUL-2006	Blinded medwatch	N/A	X	N/A
0325	21-JUL-2006	Blinded Medwatch	N/A	X	N/A
0324	19-JUL-2006	Blinded Medwatch	N/A	X	N/A
0323	18-JUL-2006	Investigators H7T-MC-TAAL, H7T-EW-TAAV, H7T-MC-TABM	N/A	X	N/A
0322	18-JUL-2006	protocol H7T-MC-TABN and 900 MG white paper (no investigator)	N/A	X	N/A
0321	18-JUL-2006	Blinded Medwatch	N/A	X	N/A
0320	12-JUL-2006	Correspondence: Request for Clarification of FDA Minutes from June 20, 2006 Type B Meeting and Submission of Sponsor	N/A	X	N/A

		Meeting Summary			
0319	11-JUL-2006	Blinded medwatch	N/A	X	N/A
0318	11-JUL-2006	Correspondence: increase in UA/NSTEMI patients for H7T-MC-TAAL	N/A	X	N/A
0317	05-JUL-2006	Blinded Medwatches	N/A	X	N/A
0316	30-JUN-2006	Request to Regulator: Type C Meeting Request	N/A	X	N/A
0315	30-JUN-2006	Blinded Medwatch	N/A	X	N/A
0314	22-JUN-2006	Investigators H7T-MC-TABM	N/A	X	N/A
0313	20-JUN-2006	Investigators H7T-MC-TAAL	N/A	X	N/A
0312	20-JUN-2006	Blinded Medwatch	N/A	X	N/A
0311	15-JUN-2006	Blinded Medwatch	N/A	X	N/A
0310	13-JUN-2006	Correspondence: Communication of DMC Recommendation for H7T-MC-TAAL	N/A	X	N/A
0309	09-JUN-2006	General Correspondence: IND Annual Report (Jan 6, 2006, Serial No. 235) Omissions and Corrections	N/A	X	N/A
0308	08-JUN-2006	Blinded Medwatch	N/A	X	N/A
0307	07-JUN-2006	Clinical Study Report H7T-EW-TAAP	N/A	X	N/A
0306	06-JUN-2006	Blinded Medwatch	N/A	X	N/A
0305	01-JUN-2006	Blinded Medwatch	N/A	X	N/A
0304	31-MAY-2006	Blinded Medwatch	N/A	X	N/A
0303	26-MAY-2006	Investigator's Brochure NI1129	N/A	X	N/A
0302	25-MAY-2006	Blinded Medwatch	N/A	X	N/A
0301	25-MAY-2006	Briefing Document for Pre-Phase 3 Meeting on June 20, 2006 to Discuss Study TABY	N/A	X	N/A
0300	24-MAY-2006	Updated Data Monitoring Committee Charter (DMC), Revision 3, for H7T-MC-TAAL	N/A	X	N/A
0299	23-MAY-2006	Blinded Medwatch	N/A	X	N/A
0298	19-MAY-2006	Investigators H7T-MC-TAAL & H7T-EW-TAAX	N/A	X	N/A
0297	18-MAY-2006	Blinded Medwatch	N/A	X	N/A
0296	16-MAY-2006	Blinded Medwatch	N/A	X	N/A
0295	16-MAY-2006	Initial Protocol H7T-MC-TABL, Protocol Amendment H7T-MC-TABL(a) and Protocol Amendment Summary H7T-MC-TABL(a), 150 mg dose justification document. Patients will be enrolled under H7T-MC-TABL(a) - no investigator sent with this protocol.	N/A	X	N/A

0294	12-MAY-2006	Blinded Medwatch	N/A	X	N/A
0293	11-MAY-2006	Blinded medwatch	N/A	X	N/A
0292	04-MAY-2006	Blinded Medwatch	N/A	X	N/A
0291	03-MAY-2006	Blinded Medwatch	N/A	X	N/A
0290	02-MAY-2006	Request to Regulator: Type B Meeting Request	N/A	X	N/A
0289	02-MAY-2006	CMC Amendment 02 May 2006 - 5 mg dose strength	N/A	X	N/A
0288	01-MAY-2006	Protocol H7T-MC-TABM and Addendums H7T-MC-TABM(1) and H7T-MC-TAMB(2) (no investigator right now because no IRB approval yet - will be sent in later)	N/A	X	N/A
0287	28-APR-2006	Blinded Medwatch	N/A	X	N/A
0286	19-APR-2006	Investigators H7T-MC-TAAL	N/A	X	N/A
0285	18-APR-2006	Blinded Medwatch	N/A	X	N/A
0284	13-APR-2006	Correspondence: DMC 6th Safety Review	N/A	X	N/A
0283	13-APR-2006	Blinded medwatch	N/A	X	N/A
0282	12-APR-2006	Protocol Amendment H7T-EW-TABF (a) and Amendment Summary H7T-EW-TABF (a)	N/A	X	N/A
0281	06-APR-2006	Blinded medwatch	N/A	X	N/A
0280	04-APR-2006	Blinded Medwatch	N/A	X	N/A
0279	03-APR-2006	Updated Clinical Endpoint Committee Charter for H7T-MC-TAAL and summary of revisions	N/A	X	N/A
0278	03-APR-2006	Protocol H7T-EW-TAAW and investigator	N/A	X	N/A
0277	30-MAR-2006	Blinded Medwatch	N/A	X	N/A
0276	28-MAR-2006	Blinded Medwatch	N/A	X	N/A
0275	23-MAR-2006	Blinded Medwatch	N/A	X	N/A
0274	17-MAR-2003	Investigators H7T-MC-TAAL	N/A	X	N/A
0273	16-MAR-2006	Blinded Medwatch	N/A	X	N/A
0272	15-MAR-2006	Protocol H7T-MC-TABR and investigator	N/A	X	N/A
0271	14-MAR-2006	Updated Data Monitoring Committee Charter (DMC), Revision 2, for H7T-MC-TAAL	N/A	X	N/A
0270	14-MAR-2006	Blinded Medwatch	N/A	X	N/A
0269	13-MAR-2006	Protocol Amendment H7T-EW-TABW(a) and Amendment Summary H7T-EW-TABW(a)	N/A	X	N/A

0268	10-MAR-2006	Blinded Medwatch	N/A	X	N/A
0267	09-MAR-2006	Blinded Medwatch	N/A	X	N/A
0266	08-MAR-2006	Blinded Medwatch	N/A	X	N/A
0265	02-MAR-2006	Blinded Medwatch	N/A	X	N/A
0264	28-FEB-2006	Blinded Medwatch	N/A	X	N/A
0263	28-FEB-2006	Protocol Addendum H7T-MC-TAAL(3.1) containing the revision summary within the document on page 10	N/A	X	N/A
0262	23-FEB-2006	Blinded Medwatch	N/A	X	N/A
0261	23-FEB-2006	Initial Protocol H7T-EW-TABS and investigator #801	N/A	X	N/A
0260	20-FEB-2006	Clinical Investigator's Brochure	N/A	X	N/A
0259	16-FEB-2006	Blinded Medwatch	N/A	X	N/A
0258	16-FEB-2006	Investigators H7T-MC-TAAL	N/A	X	N/A
0257	14-FEB-2006	Blinded Medwatch	N/A	X	N/A
0256	09-FEB-2006	Blinded Medwatch	N/A	X	N/A
0255	09-FEB-2006	Clinical Study Main Report H7T-EW-TAAD	N/A	X	N/A
0254	07-FEB-2006	General Correspondence: Enrollment stopping of STEMI patients in the TAAL Study	N/A	X	N/A
0253	07-FEB-2006	Blinded Medwatch	N/A	X	N/A
0252	06-FEB-2006	General Correspondence: Discontinuation of Study Enrollment at Investigator Site Number 480484 Study H7T-MC-TAAL (TRITON-TIMI 38)	N/A	X	N/A
0251	06-FEB-2006	Blinded Medwatch	N/A	X	N/A
0250	03-FEB-2006	Blinded Medwatch	N/A	X	N/A
0249	02-FEB-2006	Information Amendment: Preliminary data from 24 month carcinogenicity study in mice (tox reports)	N/A	X	N/A
0248	02-FEB-2006	Blinded Medwatch	N/A	X	N/A
0247	01-FEB-2006	Blinded Medwatch	N/A	X	N/A
0246	31-JAN-2006	Blinded Medwatch	N/A	X	N/A
0245	26-JAN-2006	Blinded Medwatch	N/A	X	N/A
0244	26-JAN-2006	Updated Excluded Medication List for H7T-MC-TAAL	N/A	X	N/A
0243	24-JAN-2006	Blinded Medwatch	N/A	X	N/A

0242	23-JAN-2005	Blinded Medwatch	N/A	X	N/A
0241	19-JAN-2006	Blinded Medwatch	N/A	X	N/A
0240	19-JAN-2006	Investigators H7T-MC-TAAL, H7T-EW-TABV, H7T-EW-TABW	N/A	X	N/A
0239	18-JAN-2006	Protocol Addendum H7T-MC-TAAL (12)	N/A	X	N/A
0238	12-JAN-2006	Protocol Amendment H7T-MC-TAAL(a) and protocol amendment summary H7T-MC-TAAL(a)	N/A	X	N/A
0237	12-JAN-2006	Blinded Medwatch	N/A	X	N/A
0236	10-JAN-2006	Blinded Medwatch	N/A	X	N/A
0235	06-JAN-2006	Annual Report	N/A	X	N/A
0234	05-JAN-2006	Initial Protocol H7T-EW-TAAU and investigator	N/A	X	N/A
0233	05-JAN-2006	Blinded Medwatch's	N/A	X	N/A
0232	04-JAN-2006	Correspondence: DMC 5th Safety Review	N/A	X	N/A
0231	03-JAN-2006	Blinded Medwatch	N/A	X	N/A
0230	22-DEC-2005	New Protocol and Investigator H7T-EW-TABF	N/A	X	N/A
0229	22-DEC-2005	Blinded Medwatch Reports	N/A	X	N/A
0228	19-DEC-2005	Proposed Revised Amendment H7T-MC-TAAL(a)	N/A	X	N/A
0227	19-DEC-2005	New Investigators H7T-MC-TAAL	N/A	X	N/A
0226	16-DEC-2005	New Protocol and Investigator H7T-EW-TABW	N/A	X	N/A
0225	16-DEC-2005	New Protocol and Investigator H7T-EW-TABV	N/A	X	N/A
0224	15-DEC-2005	Blinded Medwatches	N/A	X	N/A
0223	13-DEC-2005	Blinded Medwatch	N/A	X	N/A
0222	13-DEC-2005	CEC Charter TAAL	N/A	X	N/A
0221	14-DEC-2005	Termination of Study TAAN and TAAO	N/A	X	N/A
0220	12-DEC-2005	DMC 3rd and 4th Safety Review	N/A	X	N/A
0219	12-DEC-2005	Blinded Medwatches	N/A	X	N/A
0218	08-DEC-2005	Blinded Medwatches	N/A	X	N/A
0217	07-DEC-2005	Protocol Amendment H7T-FW-TAAQ(a)	N/A	X	N/A
0216	05-DEC-	Blinded Medwatches	N/A	X	N/A

	2005				
0215	05-DEC-2005	Blinded Medwatch	N/A	X	N/A
0214	01-DEC-2005	Blinded Medwatches	N/A	X	N/A
0213	28-NOV-2005	Blinded Medwatch Reports	N/A	X	N/A
0212	23-NOV-2005	Blinded Medwatch Reports	N/A	X	N/A
0211	21-NOV-2005	Blinded Medwatch Reports	N/A	X	N/A
0210	18-NOV-2005	Investigators H7T-MC-TAAL and Change in CRO for H7T-FW-TAAQ	N/A	X	N/A
0209	10-NOV-2005	Blinded Medwatch's	N/A	X	N/A
0208	09-NOV-2005	Blinded Medwatch's	N/A	X	N/A
0207	08-NOV-2005	Blinded Medwatch's	N/A	X	N/A
0206	03-NOV-2005	Blinded Medwatch's	N/A	X	N/A
0205	02-NOV-2005	Protocol Amendment & Amendment Summary H7T-EW-TAAZ(a)	N/A	X	N/A
0204	24-OCT-2005	Blinded Medwatch's	N/A	X	N/A
0203	20-OCT-2005	Blinded Medwatch's	N/A	X	N/A
0202	19-OCT-2005	Investigators H7T-MC-TAAL and , ADME Report 2002IV-HI01 Amendment 01 Examination of Effects of LY640315 on CYP1A2 and CYP3A in Primary Cultures of Human Hepatocytes	N/A	X	N/A
0201	13-OCT-2005	Blinded Medwatch's	N/A	X	N/A
0200	06-OCT-2005	Blinded Medwatch's	N/A	X	N/A
0199	06-OCT-2005	Medwatch US_0508120681 F-1 (H7T-EW-TAAZ-001-0005)	N/A	X	N/A
0198	06-OCT-2005	New Protocol and Investigator H7T-EW-TAAX	N/A	X	N/A
0197	29-SEP-2005	Blinded Medwatch's	N/A	X	N/A
0196	22-SEP-2005	Medwatch (Blinded)	N/A	X	N/A
0195	22-SEP-2005	Medwatch US_0508120681 F-4 (H7T-EW-TAAZ-001-0005)	N/A	X	N/A
0194	15-SEP-2005	Investigators H7T-MC-TAAL	N/A	X	N/A
0193	15-SEP-2005	Medwatch US_0508120681 F3	N/A	X	N/A
0192	15-SEP-2005	Blinded Medwatch	N/A	X	N/A
0191	09-SEP-2005	Blinded Medwatch	N/A	X	N/A
0190	09-SEP-	Toxicology Reports APRC-147-095, APR-148-098, APRC-148-160,	N/A	X	N/A

	2005	APS-151-015, and Amendment APS-151-015			
0189	08-SEP-2005	Blinded Medwatch	N/A	X	N/A
0188	07-SEP-2005	Nonclinical Study Reports for hERG: SBL64-70, SBL64-27, SBL63-46	N/A	X	N/A
0187	01-SEP-2005	Blinded Medwatch	N/A	X	N/A
0186	01-SEP-2005	New Protocol and Investigator H7T-EW-TAAV	N/A	X	N/A
0185	31-AUG-2005	Clinical Investigators Brochure NI1129	N/A	X	N/A
0184	25-AUG-2005	Blinded Medwatch	N/A	X	N/A
0183	22-AUG-2005	Briefing Document for September 19, 2005 5 mg dose strength meeting	N/A	X	N/A
0182	19-AUG-2005	Investigators H7T-MC-TAAL	N/A	X	N/A
0181	18-AUG-2005	Medwatch for H7T-EW-TAAZ, US_0508120681 initial	N/A	X	N/A
0180	18-AUG-2005	Blinded Medwatch	N/A	X	N/A
0179	16-AUG-2005	ERB Address Change/Update for Investigator 782, Dr. Andres Iniguez Romo from Spain for H7T-MC-TAAL	N/A	X	N/A
0178	12-AUG-2005	INvestigator ERB Address Changes for TAAL for South Africa and Italy	N/A	X	N/A
0177	12-AUG-2005	Correspondence: Response to Questions and Request for Comment	N/A	X	N/A
0176	11-AUG-2005	Blinded Medwatch	N/A	X	N/A
0175	10-AUG-2005	Blinded Medwatch	N/A	X	N/A
0174	05-AUG-2005	Updated Excluded Medication List for H7T-MC-TAAL	N/A	X	N/A
0173	05-AUG-2005	Updated Data Monitoring Committee Charter [(RV 1)] for H7T-MC-TAAL	N/A	X	N/A
0172	04-AUG-2005	Blinded Medwatch	N/A	X	N/A
0171	29-JUL-2005	ERB Address Change for investigator for H7T-MC-TAAL- Germany site	N/A	X	N/A
0170	28-JUL-2005	Blinded Medwatch	N/A	X	N/A
0169	21-JUL-2005	Blinded Medwatch	N/A	X	N/A
0168	19-JUL-2005	Investigators H7T-MC-TAAL	N/A	X	N/A
0167	14-JUL-2005	Blinded Medwatch	N/A	X	N/A
0166	13-JUL-2005	Type C Meeting Request for 5 mg dose strength tablet	N/A	X	N/A
0165	13-JUL-2005	ERB Address Change for investigators for H7T-MC-TAAL-Germany sites	N/A	X	N/A
0164	12-JUL-2005	Blinded Medwatch	N/A	X	N/A

0163	11-JUL-2005	Initial Protocol H7T-EW-TAAZ and investigator	N/A	X	N/A
0162	11-JUL-2005	General Correspondence: Reinitiation of South African site enrollment in H7T-MC-TAAL	N/A	X	N/A
0161	07-JUL-2005	Blinded Medwatch	N/A	X	N/A
0160	06-JUL-2005	Type C Meeting Request	N/A	X	N/A
0159	06-JUL-2005	Clinical Study Report: H7T-MC-TAAH, Sending to FDA without the Appendicies (7398 pages)	N/A	X	N/A
0158	30-JUN-2005	Blinded Medwatch	N/A	X	N/A
0157	30-JUN-2005	Protocol Amendment H7T-EW-TAAT(a) and protocol amendment summary H7T-EW-TAAT(a)	N/A	X	N/A
0156	30-JUN-2005	Initial Protocol H7T-EW-TAAS and investigator, Protocol Amendment H7T-EW TAAS(a), and Protocol Amendment Summary H7T-EW-TAAS(a) - all being submitted to FDA	N/A	X	N/A
0155	30-JUN-2005	General Correspondence: DMC Recommendation - 2nd periodic safety review	N/A	X	N/A
0154	23-JUN-2005	Blinded Medwatch	N/A	X	N/A
0153	22-JUN-2005	Correspondence: Notification regarding South African Clinical Sites for Clinical Trial H7T-MC-TAAL	N/A	X	N/A
0152	21-JUN-2005	Initial Protocol H7T-FW-TAAQ and investigator	N/A	X	N/A
0151	20-JUN-2005	Investigators H7T-MC-TAAL	N/A	X	N/A
0150	20-JUN-2005	Protocol Addendum H7T-MC-TAAL(8.1) and Protocol Addendum Revision Summary	N/A	X	N/A
0149	16-JUN-2005	Blinded Medwatch	N/A	X	N/A
0148	10-JUN-2005	Blinded Medwatch	N/A	X	N/A
0147	09-JUN-2005	Blinded Medwatch	N/A	X	N/A
0146	08-JUN-2005	Correspondence: TAAL Case Report Forms (Quality of Life Subsection Only)	N/A	X	N/A
0145	02-JUN-2005	US_0505117894 I US_0505116644 F US_0505117495 F EWC050343355 F EWC050443768 F EWC050543951 F	N/A	X	N/A
0144	01-JUN-2005	Investigators H7T-MC-TAAL	N/A	X	N/A
0143	31-MAY-2005	Protocol Addendum H7T-MC-TAAL(11)	N/A	X	N/A
0142	31-MAY-2005	Correspondence: Communication of DMC recommendation for H7T-MC-TAAL	N/A	X	N/A
0141	26-MAY-2005	Blinded Medwatch	N/A	X	N/A
0140	19-MAY-2005	Blinded Medwatch	N/A	X	N/A
0139	19-MAY-2005	Investigators H7T-MC-TAAL	N/A	X	N/A
0138	18-MAY-2005	Clinical Endpoint Committee (CEC) Charter	N/A	X	N/A

0137	17-MAY-2005	Blinded Medwatch amended follow up report (CA_050408013 F)	N/A	X	N/A
0136	16-MAY-2005	Correspondence: Special Protocol Assessment (SPA) for TAAL (addendum 11)	N/A	X	N/A
0135	12-MAY-2005	Blinded Medwatch	N/A	X	N/A
0134	11-MAY-2005	Statistical Analysis Plan (SAP), Final Draft	N/A	X	N/A
0133	05-MAY-2005	Blinded Medwatch	N/A	X	N/A
0132	04-MAY-2005	Investigators Protocol H7T-MC-TAAL	N/A	X	N/A
0131	28-APR-2005	Blinded Medwatch	N/A	X	N/A
0130	28-APR-2005	Protocol Amendment H7T-EW-TAAO(c) and protocol amendment summary TAAO(c)	N/A	X	N/A
0129	21-APR-2005	Blinded Medwatch	N/A	X	N/A
0128	19-APR-2005	Investigators H7T-MC-TAAL	N/A	X	N/A
0127	18-APR-2005	Clinical Study Report H7T-EW-TAAK	N/A	X	N/A
0126	15-APR-2005	Protocol Addendum H7T-MC-TAAL(6) & (9)	N/A	X	N/A
0125	15-APR-2005	Protocol H7T-EW-TAAT and investigator 001	N/A	X	N/A
0124	15-APR-2005	Protocol Addenda H7T-MC-TAAL(7) and (10)	N/A	X	N/A
0123	14-APR-2005	Blinded Medwatch	N/A	X	N/A
0122	08-APR-2005	Blinded Medwatch	N/A	X	N/A
0121	07-APR-2005	Blinded Medwatch	N/A	X	N/A
0120	04-APR-2005	Investigators TAAL	N/A	X	N/A
0119	01-APR-2005	Meeting Minutes 24-Mar-2005: teleconference with Dr. James Hung	N/A	X	N/A
0118	29-MAR-2005	General Correspondence: Response to Agency questions on protocol H7T-EW-TAAR	N/A	X	N/A
0117	31-MAR-2005	Blinded Medwatch	N/A	X	N/A
0116	29-MAR-2005	Protocol Addendum H7T-MC-TAAL(5)	N/A	X	N/A
0115	22-MAR-2005	Correspondence: Clarification of Agency Comments on the Statistical Analysis Plan for trial H7T-MC-TAAL	N/A	X	N/A
0114	18-MAR-2005	Investigators TAAL	N/A	X	N/A
0113	16-MAR-2005	CRF's (Case Report Forms)	N/A	X	N/A
0112	16-MAR-2005	H7T-EW-TAAR Contract Research Organization Information	N/A	X	N/A
0111	10-MAR-	Blinded Medwatch	N/A	X	N/A

	2005				
0110	07-MAR-2005	Protocol Amendment TAAO(b) and protocol amendment summary	N/A	X	N/A
0109	01-MAR-2005	Protocol Addendum H7T-MC-TAAL(8): The Effect of Pravastatin Versus High-Dose Atorvastatin on Platelet Aggregation in Subjects Treated with Prasugrel or Clopidogrel - Substudy	N/A	X	N/A
0108	28-FEB-2005	New Protocol H7T EW TAAP with investigator #801	N/A	X	N/A
0107	22-FEB-2005	Protocol Amendment H7T-EW-TAAO(a) and amendment summary	N/A	X	N/A
0106	22-FEB-2005	Protocol Amendment H7T-EW-TAAN(a) and amendment summary	N/A	X	N/A
0105	18-FEB-2005	New Investigators H7T-MC-TAAL	N/A	X	N/A
0104	18-FEB-2005	Additional Briefing Document materials: TFL Templates	N/A	X	N/A
0103	16-FEB-2005	Briefing Document: Statistical Analysis Plan	N/A	X	N/A
0102	10-FEB-2005	Blinded Medwatch	N/A	X	N/A
0101	02-FEB-2005	Request to FDA to remove Type B Meeting Request (Stat) sent in on Jan 21, 2005, SN098.	N/A	X	N/A
0100	28-JAN-2005	Initial Protocol H7T-EW-TAAR and investigator 001	N/A	X	N/A
0099	27-JAN-2005	CMC Amendment	N/A	X	N/A
0098	21-JAN-2005	Type B Meeting Request	N/A	X	N/A
0097	18-JAN-2005	New Investigators for H7T-MC-TAAL	N/A	X	N/A
0096	12-JAN-2005	Annual Report	N/A	X	N/A
0095	06-JAN-2005	CM&C Briefing Document for meeting with FDA Division 110 on Jan 25, 2004.	N/A	X	N/A
0094	17-DEC-2004	Investigator TAAL	N/A	X	N/A
0093	16-DEC-2004	Initial Protocol H7T-EW-TAAO and new investigator	N/A	X	N/A
0092	16-DEC-2004	Initial Protocol H7T-EW-TAAN and new Investigator	N/A	X	N/A
0091	14-DEC-2004	December 9, 2004 EOP2A meeting minutes and slides	N/A	X	N/A
0090	07-DEC-2004	Data Monitoring Committee Charter	N/A	X	N/A
0089	01-DEC-2004	CM&C Type B EOP2 Meeting Request	N/A	X	N/A
0088	16-NOV-2004	Protocol Addendum 3 for TAAL - Quality of Life Substudy	N/A	X	N/A
0087	09-NOV-2004	Briefing Document for EOP2A Meeting	N/A	X	N/A
0086	04-NOV-2004	Protocol Addendums for H7T-MC-TAAL (2) and (4)	N/A	X	N/A
0085	29-OCT-	New Protocol and investigator for H7T-MC-TAAL	N/A	X	N/A

	2004				
0084	22-OCT-2004	General Correspondance about Adverse Reporting for TAAL protocol	N/A	X	N/A
0083	13-OCT-2004	SPA Response Briefing Document	N/A	X	N/A
0082	08-OCT-2004	CM&C	N/A	X	N/A
0081	06-OCT-2004	General Correspondance: Type A Meeting Request	N/A	X	N/A
0080	24-SEP-2004	Request for Correction of FDA EOP2 Meeting Minutes	N/A	X	N/A
0079	18-AUG-2004	Special Protocol Assessment for Clinical Protocol TAAL	N/A	X	N/A
0078	13-AUG-2004	End of Phase 2A Meeting Request	N/A	X	N/A
0077	11-AUG-2004	CIB NI1129	N/A	X	N/A
0076	11-AUG-2004	End of Phase 2 Meeting Minutes	N/A	X	N/A
0075	21-JUL-2004	ADME Report 009D03 and TAAJ Clinical Study Main Report	N/A	X	N/A
0074	15-JUL-2004	End of Phase II Breifing Document for meeting on August 4th, 2004.	N/A	X	N/A
0073	20-MAY-2004	Clinical Study Report H7T-EW-TAAI	N/A	X	N/A
0072	27-APR-2004	EOP2 Meeting Request	N/A	X	N/A
0071	09-APR-2004	CT Labels for H7T-EW-TAAK	N/A	X	N/A
0070	01-APR-2004	ADMR Report for Study 010R03	N/A	X	N/A
0069	22-MAR-2004	EOP 2 Meeting Request	N/A	X	N/A
0068	01-MAR-2004	ATR-149-081 Dated March 13, 2003. Dog Study with salts HCL and Maleate salt. ADME Reports 007M03	N/A	X	N/A
0067	26-FEB-2004	Medwatch H7T-MC-TAAH	N/A	X	N/A
0066	20-FEB-2004	Clinical Study main Report for Study H7T-EW-TAAF	N/A	X	N/A
0065	02-FEB-2004	H7T-LC-TAAB Clinical Study Report	N/A	X	N/A
0064	21-JAN-2004	ADME Report for Study 2003IV-EI001 on Cytochromes P450, Formation of R-138727	N/A	X	N/A
0063	15-JAN-2004	Medwatch (Blinded Safety Report)	N/A	X	N/A
0062	14-JAN-2004	Annual Report	N/A	X	N/A
0061	24-DEC-2003	Blinded Safety Report (Medwatch)	N/A	X	N/A
0060	19-DEC-2003	New Protocol H7T-EW-TAAK	N/A	X	N/A
0059	18-DEC-2003	Medwatch (Blinded IND Safety Reports)	N/A	X	N/A

0058	02-DEC-2003	Clinical Study Main Report for Study H7T-EW-TAAG	N/A	X	N/A
0057	19-NOV-2003	IND Safety Reports (Blinded)	N/A	X	N/A
0056	13-NOV-2003	Blinded Medwatch (IND Safety Reports)	N/A	X	N/A
0055	07-NOV-2003	Meeting Minutes for Protocol Guidance Meeting held October 16, 2003.	N/A	X	N/A
0054	06-NOV-2003	Blinded Medwatch (IND Safety Report)	N/A	X	N/A
0053	30-OCT-2003	IND Safety Reports (2 Blinded Medwatch Reports)	N/A	X	N/A
0052	24-OCT-2003	H7T-MC-TAAH Investigator	N/A	X	N/A
0051	16-OCT-2003	Blinded Medwatch (2) (IND Safety Reports)	N/A	X	N/A
0050	14-OCT-2003	Protocol Amendment H7T-MC-TAAH(a)	N/A	X	N/A
0049	09-OCT-2003	MedWatch Blinded	N/A	X	N/A
0048	02-OCT-2003	IND Safety Reports (Medwatch (4) Blinded)	N/A	X	N/A
0047	25-SEP-2003	IND Safety Reports (2 Blinded Medwatch)	N/A	X	N/A
0046	24-SEP-2003	Investigators H7T-MC-TAAH	N/A	X	N/A
0045	24-SEP-2003	CS-747 Briefing Document 24 September 2003	N/A	X	N/A
0044	18-SEP-2003	(2) IND Safety Reports (Blinded Medwatch)	N/A	X	N/A
0043	11-SEP-2003	MedWatch	N/A	X	N/A
0042	04-SEP-2003	Medwatch	N/A	X	N/A
0041	27-AUG-2003	Addendum for Study H7T-MC-TAAH (5)	N/A	X	N/A
0040	21-AUG-2003	IND MedWatch(IND Safety Report)	N/A	X	N/A
0039	19-AUG-2003	Investigators for Study H7T-MC-TAAH	N/A	X	N/A
0038	18-AUG-2003	Meeting Request for Pe-Phase 3 Study Design Discussion for Treatment of PCI.	N/A	X	N/A
0037	07-AUG-2003	Medwatch	N/A	X	N/A
0036	22-JUL-2003	Correspondence Request for Special CAC Protocol Assessment	N/A	X	N/A
0035	02-JUL-2003	H7T-MC-TAAH Investigators	N/A	X	N/A
0034	13-JUN-2003	Investigators TAAH, CT Labels H7T-MC-TAAH	N/A	X	N/A
0033	10-JUN-2003	Protocol Amendments H7T-EW-TAAD(a)(b)	N/A	X	N/A
0032	09-JUN-2003	CS-747 Protocol Dose Summary and Justification and a Special	N/A	X	N/A

		Protocol Assessment (Included were Tox Reports, APRC-149-045, APRC-147-013, B-4987, B-5010, B-4990)			
0031	16-MAY-2003	Investigators H7T-MC-TAAH, CT Labels H7T-MC-TAAH, H7T-EW-TAAF, H7T-EW-TAAI	N/A	X	N/A
0030	05-MAY-2003	INFORMATION AMENDMENT: NOTIFICATION OF PLANNED CARCINOGENICITY PROTOCOL SUBMISSION	N/A	X	N/A
0029	01-MAY-2003	Response to FDA Questions, Reference study H7T-EW-TAAE	N/A	X	N/A
0028	15-APR-2003	DSMB Information Amendment	N/A	X	N/A
0027	07-APR-2003	Investigators and Protocols for studies H7T-EW-TAAF, H7T-EW-TAAI, and New Investigators for Study H7T-MC-TAAH.	N/A	X	N/A
0026	31-MAR-2003	Investigators H7T-MC-TAAH	N/A	X	N/A
0025	24-MAR-2003	Toxicology Report No. 02 and Toxicology Report No. 03, Toxicology studies BOZO/B-4987, B-4989, B-4990, BOZO/B-5010	N/A	X	N/A
0024	14-MAR-2003	CM&C Information Amendment for HCL Tablet, CS-747	N/A	X	N/A
0023	26-FEB-2003	Protocol H7T-MC-TAAH, Protocol Addendum H7T-MC-TAAH (1:Quantitative QT Interval Determinations, and Protocol Addendum H7T-MC-TAAH (2: Pharmacokinetic)	N/A	X	N/A
0022	19-FEB-2003	ADME Report No.03, ADME Report No.04	N/A	X	N/A
0021	31-JAN-2003	CT Labels H7T-EW-TAAD	N/A	X	N/A
0020	14-JAN-2003	Annual Report and CIB	N/A	X	N/A
0019	08-JAN-2003	Response to FDA for Request for Information: Study H7T-EW-TAAG and PK Data	N/A	X	N/A
0018	12-DEC-2002	Response to FDA Request for Information TAAG	N/A	X	N/A
0017	02-DEC-2002	CT Labels	N/A	X	N/A
0016	19-NOV-2002	Clinical Study Main Report for study H7T-LC-TAAC, Phase 1 and Clinical Study Main Report for study H7T-EW-TAAE. ADME reports 01 and 02.	N/A	X	N/A
0015	18-SEP-2002	Do not Use, Dummy Packet Holding for a Note to File. Follow-up w/ Leslie for NTF was on 01-15-04. Serial No. 015 needed to be skipped due to a phone call from Margaret Pease-Fye to Leslie Carter. The archives were not in error, the reason is unknown for the change of serial no. 015 (which was submitted to the FDA and submitted in RCOS) to 016 is unknown. The submission dated 19-Nov-2002 was moved to another packet and given the serial no. 016, however, the assembly is still labeled serial no. 015 in docman.	N/A	X	N/A
0014	11-NOV-2002	CM&C Information Amendment CS-747 Placebo Tablets	N/A	X	N/A
0013	08-NOV-2002	IND Information Amendment: Clinical results of H7T-EW-TAAG, November 8, 2002.	N/A	X	N/A
0012	31-OCT-2002	Protocol H7T-EW-TAAD, Investigators from EW, and CM&C Amendment	N/A	X	N/A
0011	24-SEP-2002	EOP 1 Meeting Minutes	N/A	X	N/A
0010		Serial Number 10 inadvertently missed.	N/A	X	N/A

0009	28-AUG-2002	Briefing Document for the End of Phase 1. Meeting on Sept. 20, 2002.	N/A	X	N/A
0008	28-AUG-2002	(PDF Files from Sankyo)Toxicity B-4593 Report, Pharmacokinetic Reports ATRC-148-007, ATRC-148-008, ATRC 148-010, ATRC-148-046, ATRC-148-11, and CIB Study NI1129	N/A	X	N/A
0007	07-AUG-2002	CMC Amendment	N/A	X	N/A
0006	31-JUL-2002	Clinical Study Main Report H7T-EW-TAAA, Phase 1	N/A	X	N/A
0005	27-JUN-2002	Medwatch	N/A	X	N/A
0004	25-JUN-2002	New Protocol, New Investigator H7T EW TAAG 001,and CM&C Information Amendment	N/A	X	N/A
0003	04-JUN-2002	Faxed Correspondence,will submit at a later date, Request for a tye B Meeting, End of Phase 1	N/A	X	N/A
0002	09-MAY-2002	Informational IND Amendment to support Carbon-14 study and Protocol H7T-LC-TAAB	N/A	X	N/A
0001	22-FEB-2002	Tox Report 01 for CS-747	N/A	X	N/A
0000	16-OCT-2001	Initial IND Submission for CS-747	N/A	X	N/A

EXHIBIT 8
NDA LOG

Registration Number 22-307
Roadmap Information

Sponsor's Serial Number	Sponsor's Submission Date	Description of Submission	CD Serial Number	Paper Only	File or Folder Name
0116	15-JUL-2009	Seq#0116: Cross Reference Tox Report CCGS03 Amendment 02 to IND 63,449	N/A	X	N/A
0115	13-JUL-2009	Seq#0115: Final Carton and Container Labels	N/A	X	N/A
0114	15-JUL-2009	Seq#0114: Response REMS Documents Introductory Letter and HCP Brochure	N/A	X	N/A
0113	13-JUL-2009	Seq#0113: Final SPL	N/A	X	N/A
0112	10-JUL-2009	Seq#0112: Response Post-Marketing Commitment Dates	N/A	X	N/A
0111	09-JUL-2009	Seq#0111: Response to FDA Request Introductory Letter and REMS 5	N/A	X	N/A
0110	09-JUL-2009	Seq#0110: Response to FDA Request Updated USPI	N/A	X	N/A
0109	09-JUL-2009	Seq#0109: Response REMS 4, Introductory Letter, and HCP Brochure	N/A	X	N/A
0108	08-JUL-2009	Seq#0108: Regulatory Response Post Marketing Requirement Dates, Post Marketing Commitment Dates	N/A	X	N/A
0107	08-JUL-2009	Seq#0107: Response to FDA Request Updated Draft USPI	N/A	X	N/A
0106	25-JUN-2009	Seq#0106: Response to FDA Request Intro Letter Clean, Intro Letter Track Changes, Prescribers Brochure, Prescribers Overview	N/A	X	N/A
0105	23-JUN-2009	Seq#0105: Response to FDA Request June 18, 2009	N/A	X	N/A
0104	12-JUN-2009	Seq#0104: Revised Medication Guide Replacing Seq0101	N/A	X	N/A
0103	10-JUN-2009	Seq#0103: Labeling Response Replacing Sequence 0093	N/A	X	N/A
0102	22-MAY-2009	Seq#0102: Regulatory Response Table 2 and Stent Label	N/A	X	N/A
0101	21-MAY-2009	Seq#0101: Response and Draft Labeling Revised Medication Guide	N/A	X	N/A
0097	13-MAR-2009	Seq#0097: Regulatory Response CMC to FDA Request March 9, 10, 11, 2009	N/A	X	N/A
0091	05-MAR-2009	Seq#0091: CM&C Regulatory Response to FDA e-mails Feb 2009	N/A	X	N/A
0005	28-JAN-2008	Sequence 0005: Response to FDA Request	N/A	X	N/A
	26-DEC-2007	Sequence 0000, 0001, 0002: New NDA eCTD	N/A	X	N/A
	09-JAN-2008	Sequence 0003: Submission of Original Protocols TAAL, TABL, TAAH	N/A	X	N/A
	15-JAN-2008	Sequence 004: Submission of Meeting Minutes and Response to FDA Questions	N/A	X	N/A
	30-JAN-2008	Sequence 0006: Response to FDA Request Datasets	N/A	X	N/A
	04-FEB-2008	Sequence 0007: Response to FDA Request for Information from January 28, 2008	N/A	X	N/A
	06-FEB-2008	Sequence 0008: Response to FDA Request 01 Feb 2008 Study TAAL Investigator Information	N/A	X	N/A

	19-FEB-2008	Sequence 0009: Response to FDA Request Drived DataSets for TAAZ	N/A	X	N/A
	25-FEB-2008	Sequence 0010: Response to FDA Request February 20, 2008 for TAAZ TAAL Datasets and Raw Files for Randomization List and IVRS System	N/A	X	N/A
	28-FEB-2008	Sequence 0011: Response to FDA Request TAAF	N/A	X	N/A
	20-MAR-2008	Sequence 0012: Response to Request for Information Response Documents and Case Report Forms	N/A	X	N/A
	20-MAR-2008	Sequence 0013: Response Labeling to 74-Day Letter	N/A	X	N/A
	21-MAR-2008	Sequence 0014: Response Neoplasm Datasets and CRFs	N/A	X	N/A
	24-MAR-2008	Sequence 0015: Meeting Minutes Teleconference March 17, 2008	N/A	X	N/A
	25-MAR-2008	Sequence 0016: Response Neoplasm Report and 74-Day Letter	N/A	X	N/A
	27-MAR-2008	Sequence 0017: Response Follow-up to March 21, 2008 e-mail Communication from FDA Neoplasms and CRFs	N/A	X	N/A
	02-APR-2008	Sequence 0018: Meeting Minutes 28 March 2008	N/A	X	N/A
	07-APR-2008	Sequence 0019: Response to FDA Request TAAL Withdrawal of Consent, SAS Datasets, Data Definitiaon Document, and Annotated CRF	N/A	X	N/A
	07-APR-2008	Sequence 0020: Response to FDA Request to Question 3b and 3c of the 74-day Letter Received March 7, 2008	N/A	X	N/A
	14-APR-2008	Sequence 0021: Response to FDA Request 09 Apr 2008 Related to PPMI Location Within the CSR	N/A	X	N/A
	15-APR-2008	Sequence 0022: 120 Safety Update Report Synopsis H7T-MC-TABN-TABM	N/A	X	N/A
	17-APR-2008	Sequence 0023: Response to FDA Request for Additional Information to Two e-Mails for 09 Apr 2008 and Two e-Mails for 14 Apr 2008	N/A	X	N/A
	22-APR-2008	Sequence 0024: Response to FDA Request Dated April 14 and 17 2008 for Clarification Regarding Adverse Event Datasets	N/A	X	N/A
	22-APR-2008	Sequence 0025: Response to Request Teleconference on April 11 and 17, 2008	N/A	X	N/A
	24-APR-2008	Sequence 0026: Response to FDA Request CRFs TAAL	N/A	X	N/A
	24-APR-2008	Sequence 0027: Response to FDA Request 74-Day Letter Dated March 7, 2008	N/A	X	N/A
	25-APR-2008	Sequence 0028: Submission of April 17, 2008 Teleconference Minutes	N/A	X	N/A
	28-APR-2008	Sequence 0029: Response to FDA Requests on April 24, 25, 2008	N/A	X	N/A
	30-APR-2008	Sequence 0030: Response to FDA Request March 7, 2008 Endpoint Datasets	N/A	X	N/A
	30-APR-2008	Sequence 0031: Submission of Data Define Document TAAL	N/A	X	N/A
	30-APR-2008	Sequence 0032: CMC(DR) Response to FDA Letter Dated April 9, 2008	N/A	X	N/A
	06-MAY-2008	Sequence 0033: Response to FDA Request Includes a TOSNP, Neoplasm CRF, Neoplasm Datasets and Corresponding Data Define Document	N/A	X	N/A

	09-MAY-2008	Sequence 0034: Response Neoplasm Case Report Forms	N/A	X	N/A
	09-MAY-2008	Sequence 0035: Response Neoplasm Summary	N/A	X	N/A
	09-MAY-2008	Sequence 0036: Regulatory Response to e-Mail From FDA May 1, 2008	N/A	X	N/A
	12-MAY-2008	Sequence 0037: CMC Meeting Minutes	N/A	X	N/A
	12-MAY-2008	Sequence 0038: Regulatory Response Assay Validation Reports and Pharmacodynamic Methods	N/A	X	N/A
	14-MAY-2008	Sequence 0039: Updates to Proposed Cartons, Labels, and Blister	N/A	X	N/A
	16-MAY-2008	Sequence 0040: Regulatory Response to March 13, 2008 FDA Reguest TAAL Lot Numbers	N/A	X	N/A
	10-JUN-2008	Sequence 0041: Response to FDA Teleconferenc June 4, 2008	N/A	X	N/A
	11-JUN-2008	Sequence 0042: Submission Cartons and Labels	N/A	X	N/A
	04-JUN-2008	PG51957 Coming soon journal ad	N/A	X	N/A
	17-JUN-2008	Sequence 0043: Regulatory Response Reference Sequence 0041 Submitted June 10, 2008	N/A	X	N/A
	20-JUN-2008	Sequence 0044: Post Marketing Proposals	N/A	X	N/A
	20-JUN-2008	Sequence 0045: Regulatory Response Request June 19, 2008	N/A	X	N/A
	25-JUN-2008	Sequence 0046: Submission of Container Label	N/A	X	N/A
	25-JUN-2008	Sequence 0047: Regulatory Response Request June 23, 2008	N/A	X	N/A
	22-JUL-2008	Sequence 0048: Response to FDA Request ECG and Angiogram	N/A	X	N/A
	30-JUL-2008	Sequence 0049: Draft Labeling	N/A	X	N/A
	08-AUG-2008	Sequence 0050: Response to FDA Request on August 6, 2008	N/A	X	N/A
	14-AUG-2008	Sequence 0051: Response to FDA Request August 11, 2008	N/A	X	N/A
	19-AUG-2008	Sequence 0052: CMC Response FDA Request August 15, 2008	N/A	X	N/A
	07-AUG-2008	PG53393 Effient coming soon banner ad	N/A	X	N/A
	25-AUG-2008	Sequence 0053: Regulatory Response Stent Thrombosis Justification with TIMI and Cutlip	N/A	X	N/A
	28-AUG-2008	Sequence 0055: Regulatory Response to FDA Request Dated August 21, 2008	N/A	X	N/A
	04-SEP-2008	Sequence 0054: Regulatory Response Questions on CABG Bleeding Tables: TAAL Report	N/A	X	N/A
	11-SEP-2008	Sequence 0056: Response to FDA Request on September 11, 2008	N/A	X	N/A
	18-SEP-2008	Sequence 0057: Regulatory Response Reference Meeting September 15, 2008 and FDA Request September 17, 2008	N/A	X	N/A
	22-SEP-2008	Sequence 0058: Regulatory Response White Paper Neoplasm	N/A	X	N/A
	24-SEP-2008	Sequence 0059: Regulatory Response White Paper on Benefit Risk and Response to Questions on September 19, 2008	N/A	X	N/A
	26-SEP-2008	Sequence 0060: Regulatory Response Listing Malignancy Deaths	N/A	X	N/A

	03-OCT-2008	Sequence 0062: Response to September 30, 2008 Request PPMI	N/A	X	N/A
	03-OCT-2008	Sequence 0061: Response Reference to September 24, 2008 Meeting	N/A	X	N/A
	10-OCT-2008	Sequence 0063: Response to FDA Request October 7, 2008 Preclinical	N/A	X	N/A
	10-OCT-2008	Sequence 0064: Response Data Reconciliation	N/A	X	N/A
	16-OCT-2008	Sequence 0065: Type A Meeting Request for Meeting with Dr. Mohab Nasr	N/A	X	N/A
	04-NOV-2008	Sequence 0066: Meeting Minutes 29 Oct 2008 and Regulatory Response Regarding Potential Xenograft Studies	N/A	X	N/A
	12-NOV-2008	Sequence 0067: Regulatory Response Includes Datasets, Data Definition Document, and Meeting Minutes from October 29, 2008 Meeting	N/A	X	N/A
	17-NOV-2008	Sequence 0068: Meeting Minutes November 14, 2008	N/A	X	N/A
	07-NOV-2008	PG54386 AHA plasma screen ad PG54001 AHA electronic ads PG54939 AHA sponsorship items PG54944 AHA distribution rack	N/A	X	N/A
	21-NOV-2008	Sequence 0071: Request for Clarification on FDA Meeting Minutes	N/A	X	N/A
	13-NOV-2008	Sequence 0070: MedGuide and REMS Update	N/A	X	N/A
	03-DEC-2008	Sequence 0072: TAAL 02 Clinical Report Addendum 1	N/A	X	N/A
	11-DEC-2008	Sequence 0073: Regulatory Response TAAL to FDA Request December 5, 2008	N/A	X	N/A
	05-DEC-2008	Sequence 0069: FDA Request for Supplement Stent Thrombosis Report	N/A	X	N/A
	18-DEC-2008	Sequence 0074: Response to Request About Dissolution Method	N/A	X	N/A
	18-DEC-2008	Sequence 0076: Response Meeting Minutes Requested	N/A	X	N/A
	23-DEC-2008	Sequence 0077: Response to Request for Additional Analyses Conducted in Response to Questions from CHMP	N/A	X	N/A
	05-JAN-2009	Sequence 0078: Response to Request about Tumor Progression Studies	N/A	X	N/A
	01-JAN-2009	Sequence 0075: Advisory Committee Briefing Document	N/A	X	N/A
	07-JAN-2009	Sequence 0079: Advisory Committee Revised Briefing Document for February 3, 2009 Meeting	N/A	X	N/A
	15-JAN-2009	Sequence 0081: Regulatory Response for Stent Thrombsis, Clinical Trial Material TABY, Xenograft Study	N/A	X	N/A
	19-JAN-2009	Sequence 0080: Response to FDA Request REMS Proposal	N/A	X	N/A
	20-JAN-2009	Sequence 0082: Neoplasm Response to FDA Request January 16, 2009	N/A	X	N/A
	23-JAN-2009	Sequence 0083: CMC Response Redaction	N/A	X	N/A
	27-JAN-2009	Sequence 0085: Response to FDA Briefing Document Request ERRATA Report	N/A	X	N/A
	27-JAN-2009	Sequence 0086: Response to FDA Request vitro and vivo Study Protocols	N/A	X	N/A
	29-JAN-2009	Sequence 0084: Response to FDA Request on January	N/A	X	N/A

		26, 2009			
	06-FEB-2009	Sequence 0087: Regulatory Response Nonclinical Pharmacology Report CCGS03	N/A	X	N/A
	12-FEB-2009	Sequence 0088: Response Advisory Committee Slides	N/A	X	N/A
	13-FEB-2009	Sequence 0089: Revised Carton and Label	N/A	X	N/A
	19-FEB-2009	Sequence 0092: Response to FDA Request September 26, 2008 Study TAAL	N/A	X	N/A
	23-FEB-2009	Sequence 0090: Regulatory Response Stent Thrombosis	N/A	X	N/A
	10-MAR-2009	Sequence 0094: Response TABY (TRILOGY) Malignancy	N/A	X	N/A
	11-MAR-2009	Sequence 0095: Regulatory Response Carton and Labeling	N/A	X	N/A
	10-MAR-2009	Sequence 0093: Regulatory Response Proposed Labeling	N/A	X	N/A
	12-MAR-2009	Sequence 0096: Regulatory Response REMS Program and Supporting Information	N/A	X	N/A
	23-MAR-2009	Sequence 0098: Response to FDA Request March 18, 2009 Draft Labeling	N/A	X	N/A
	24-APR-2009	Seq#0099: CMC Response to General Correspondence From FDA Dated April 3, 2009	N/A	X	N/A
	04-MAY-2009	Seq#0100: Response to FDA Comments April 15, 2009 Updated REMS Document Replacing Seq#0096	N/A	X	N/A